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U.S. Department of Health & Human Services

Food and Drug Administration

SAVE REQUEST

USER:	(smw)
FOLDER:	K121214 - 2783 pages
COMPANY:	BECKMAN COULTER, INC. (BECKCOUL)
PRODUCT:	IMMUNOASSAY METHOD, TROPONIN SUBUNIT (MMI)
SUMMARY:	Product: ACCESS ACCUTNI+3 REAGENT AND ACCESS ACCUTN1+3 CALIBRATORS FOR USE ON T
DATE REQUESTED:	Jul 27, 2015
DATE PRINTED:	Jul 27, 2015
Note:	Printed

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration

Memorandum

Date: 7/3/13

From: DMC (HFZ-401)

Subject: Premarket Notification Number(s): K121214/A2

To: Division Director: CH/CRDB/DCTD

The attached information has been received by the 510(k) DMC on the above referenced 510(k) submission(s). Since a final decision has been rendered, this record is officially closed.

Please review the attached document and return it to the DMC, with one of the statements checked below.

_____ Information does not change the status of the 510(k); no other action required by the DMC; please add to image file. (Prepare K-25) THIS DOES NOT APPLY TO TRANSFER OF OWNERSHIP. PLEASE BRING ANY TRANSFER OF OWNERSHIP TO POS.

_____ Additional information requires a new 510(k); however, the information submitted is incomplete; (Notify company to submit a new 510(k); [Prepare the K30 Letter on the LAN]

X No response necessary (e.g., hard copy of fax for the truthful and accuracy statement, 510(k) statement, change of address, phone number, or fax number).

CLIA CATEGORIZATION refers to laboratory test system devices reviewed by the Division of Clinical Laboratory Devices (HFZ-440

_____ Information requires a **CLIA CATEGORIZATION**; the complexity may remain the same as the original 510(k) or may change as a result of the additional information (Prepare a CAT letter) PVV.

_____ Additional information requires a **CLIA CATEGORIZATION**; however, the information submitted is incomplete; (call or fax firm)

X No response necessary

This information should be returned to the DMC within 10 working days from the date of this Memorandum.

Reviewed by: Paula V. Capasino

Date: 8/5/13

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FDA CDRH DMC
JUL 03 2013
Received

K121214

BECKMAN COULTER

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: CLIA Categorization Request

Dear Madam/Sir:

Beckman Coulter Inc. is submitting the attached documentation to request a CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i system based on 42 CFR 493.15(b) of the CLIA 1988 regulation.

The UniCel DxC 600i system was cleared on February 27, 2006 under k060256. The UniCel DxC 600i system contains an Access 2 Immunoassay System. Under the Reagent Replacement and Instrument Family Policy, the UniCel DxC 600i system is a member of the same instrument family as the Access 2 Immunoassay System. Access AccuTnI+3 on the Access 2 Immunoassay System was cleared by FDA on June 14, 2013 under k121214 and found to be CLIA moderately complex.

A description of the product is provided, in addition to the draft Instructions for Use. The e-copy of this response is an exact duplicate of the paper copy.

Please review this request and contact me if you have any questions.

Sincerely,

Kerrie Oetter
Senior Regulatory Affairs Analyst
Phone: (952) 368-7858
Fax: (952) 3687610
ksoetter@beckman.com

Beckman Coulter, Inc
1000 Lake Hazeltine Drive
Chaska, MN 56318-1084

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CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i

Product Description:
The Access AccuTnI+3 for Access 2 Immunoassay System (k121214) is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay system to aid in the diagnosis of myocardial infarction. The UniCel DxC 600i (k060256) incorporates an Access 2 system in its platform configuration.

The Access family of immunoassay analyzers consist of microcomputer controlled random and continuous access instruments. The analyzers perform enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction.

Reagent Replacement and Instrument Family:
The Access AccuTnI+3 and the UniCel DxC 600i are eligible for CLIA categorization under the *Guidance for Industry and FDA Staff; Reagent Replacement and Instrument Family Policy* (December 11, 2003). As shown in **Table 1** below, both the instrument and the reagent are 510(k) cleared.

Table 1: Reagent Replacement Regulatory Pathway

Test System Current Regulatory Status		
	Cleared	**New/not cleared**
Reagent	**A – AccuTnI+3 for Access 2 Immunoassay (k121214)**	B
Instrument	**C – UniCel DxC 600i (k060256)**	D

A+C= Replacement Reagent Policy

A summary of the premarket notification 510(k) history for the Access 2 Immunoassay Systems and their respective immunoassay and chemistry analyzer components is provided in **Table 2** below.

Table 2: 510(k) History of the Access® Immunoassay Analyzer Family

Analyzer System	FDA Docket	Clearance Date	Immunoassay Analyzer	Chemistry Analyzer
Access 2 Immunoassay Analyzer Plus AccuTnI+3	K121214	June 14, 2013	Stand-Alone	N/A
UniCel DxC 600i SYNCHRON Access Clinical System	K060256	February 27, 2006	Access 2 Immunoassay Analyzer (Access 2)	UniCel DxC 600 SYNCHRON System analyzer (DxC 600)

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CLIA Complexity Evaluation under 42 CFR 493.17(a):
A complexity categorization scoring was performed on the Access AccuTnI+3 for UniCel DxC 600i. The results of the scoring appear in **Table 3**. The categorization was based on the specific criteria outlined in 42 CFR 493.15(b) of the CLIA 1988 regulation. Using those criteria, all seven sections were assigned scores from 1 to 3, with 1 indicating the lowest level of complexity. The Access AccuTnI+3 for UniCel DxC 600i was determined to be moderately complex, having a total score of less than 12 points.

The rating of moderately complex assays is based on the rationale contained in the regulation. For this assay, the analyst needs minimal scientific and technical knowledge beyond the step-by-step directions, which may be obtained through on-the-job instruction, to properly perform the assay procedures and report results (1 point). The analyst needs minimal training and experience for the preanalytic, analytic, and postanalytic phases of the testing process to perform the assay (1 point). The Access AccuTnI+3 for UniCel DxC 600i is liquid, prepackaged, premeasured, and requires no preparation (1 point). The UniCel DxC 600i has automatic specimen processing, computer controlled timing steps, built-in function checks, and no required calculations, necessitating only periodic calibration by the analyst at the request of the software system (1 point). Calibration and control materials are readily available, stable, and easily incorporated into the procedure. Proficiency testing materials are available and stable (1 point). Troubleshooting is clearly described in instrument manuals and maintenance steps can be easily performed with appropriate training (1 point). Minimal interpretation and judgment is required on the part of the analyst as decision making is not required through the testing process itself (1 point).

Table 3: CLIA Complexity Assessment Access AccuTnI+3 on the UniCel DxC 600i

Category	Access AccuTnI+3 for use on the UniCel DxC 600i
Knowledge	1
Training	1
Reagent Preparation	1
Operational Steps	1
QC/PT Materials Availability/Stability	1
Troubleshooting & Maintenance	1
Judgment	1
Total	**7**
Interpretation	**Moderately complex**

Conclusion: Based on the information provided above Beckman Coulter concludes the AccuTnI+3 on the DxC 600i is CLIA moderately complex category.

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For CLIA Categorization Only

Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS† WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

†Access 2 and UniCel DxC 600i

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:

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- Symptoms of ischemia;
- New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

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R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.

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- For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
- Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
- If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
- Follow blood collection tube manufacturer's recommendations for centrifugation.
- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for

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information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance of the quality control material. The thermal profile of native human cardiac troponin I was used in development of this assay. Quality control materials containing troponin I not from this source (e.g. recombinant antigens) may behave differently. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[21,22] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[23,24] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[25] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.

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7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (μg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the

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diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[26] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 – 86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[27] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[28] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[29,30] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[31] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[32] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[33] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[33] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[34]

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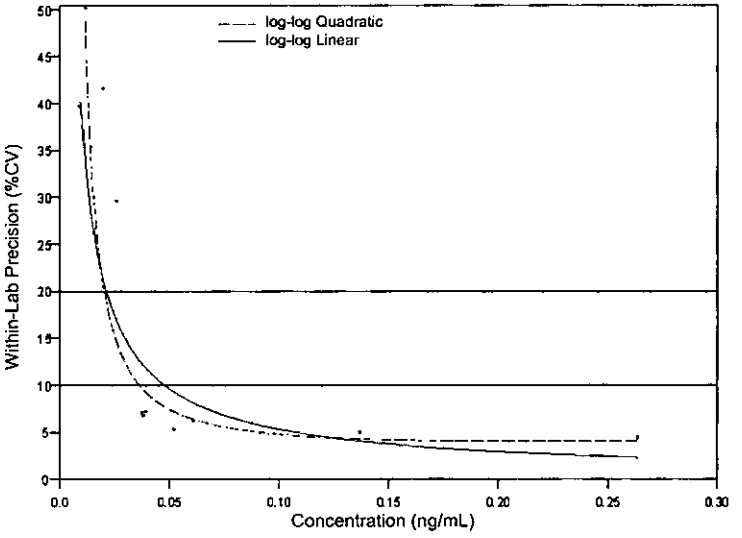
Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[34]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[34] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

Limit of Quantitation (imprecision estimate)



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Product Categorization Only

Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: CLIA Categorization Request

Dear Madam/Sir:

Beckman Coulter Inc. is submitting the attached documentation to request a CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i system based on 42 CFR 493.15(b) of the CLIA 1988 regulation.

The UniCel DxC 600i system was cleared on February 27, 2006 under k060256. The UniCel DxC 600i system contains an Access 2 Immunoassay System. Under the Reagent Replacement and Instrument Family Policy, the UniCel DxC 600i system is a member of the same instrument family as the Access 2 Immunoassay System. Access AccuTnI+3 on the Access 2 Immunoassay System was cleared by FDA on June 14, 2013 under k121214 and found to be CLIA moderately complex.

A description of the product is provided, in addition to the draft Instructions for Use. The e-copy of this response is an exact duplicate of the paper copy.

Please review this request and contact me if you have any questions.

Sincerely,

Kerrie Oetter
Senior Regulatory Affairs Analyst
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i

Product Description:
The Access AccuTnI+3 for Access 2 Immunoassay System (k121214) is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay system to aid in the diagnosis of myocardial infarction. The UniCel DxC 600i (k060256) incorporates an Access 2 system in its platform configuration.

The Access family of immunoassay analyzers consist of microcomputer controlled random and continuous access instruments. The analyzers perform enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction.

Reagent Replacement and Instrument Family:
The Access AccuTnI+3 and the UniCel DxC 600i are eligible for CLIA categorization under the *Guidance for Industry and FDA Staff; Reagent Replacement and Instrument Family Policy* (December 11, 2003). As shown in **Table 1** below, both the instrument and the reagent are 510(k) cleared.

Table 1: Reagent Replacement Regulatory Pathway

Test System Current Regulatory Status		
	Cleared	**New/not cleared**
Reagent	**A – AccuTnI+3 for Access 2 Immunoassay (k121214)**	B
Instrument	**C – UniCel DxC 600i (k060256)**	D

A+C= Replacement Reagent Policy

A summary of the premarket notification 510(k) history for the Access 2 Immunoassay Systems and their respective immunoassay and chemistry analyzer components is provided in **Table 2** below.

Table 2: 510(k) History of the Access® Immunoassay Analyzer Family

Analyzer System	FDA Docket	Clearance Date	Immunoassay Analyzer	Chemistry Analyzer
Access 2 Immunoassay Analyzer Plus AccuTnI+3	K121214	June 14, 2013	Stand-Alone	N/A
UniCel DxC 600i SYNCHRON Access Clinical System	K060256	February 27, 2006	Access 2 Immunoassay Analyzer (Access 2)	UniCel DxC 600 SYNCHRON System analyzer (DxC 600)

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

CLIA Complexity Evaluation under 42 CFR 493.17(a):
A complexity categorization scoring was performed on the Access AccuTnI+3 for UniCel DxC 600i. The results of the scoring appear in **Table 3**. The categorization was based on the specific criteria outlined in 42 CFR 493.15(b) of the CLIA 1988 regulation. Using those criteria, all seven sections were assigned scores from 1 to 3, with 1 indicating the lowest level of complexity. The Access AccuTnI+3 for UniCel DxC 600i was determined to be moderately complex, having a total score of less than 12 points.

The rating of moderately complex assays is based on the rationale contained in the regulation. For this assay, the analyst needs minimal scientific and technical knowledge beyond the step-by-step directions, which may be obtained through on-the-job instruction, to properly perform the assay procedures and report results (1 point). The analyst needs minimal training and experience for the preanalytic, analytic, and postanalytic phases of the testing process to perform the assay (1 point). The Access AccuTnI+3 for UniCel DxC 600i is liquid, prepackaged, premeasured, and requires no preparation (1 point). The UniCel DxC 600i has automatic specimen processing, computer controlled timing steps, built-in function checks, and no required calculations, necessitating only periodic calibration by the analyst at the request of the software system (1 point). Calibration and control materials are readily available, stable, and easily incorporated into the procedure. Proficiency testing materials are available and stable (1 point). Troubleshooting is clearly described in instrument manuals and maintenance steps can be easily performed with appropriate training (1 point). Minimal interpretation and judgment is required on the part of the analyst as decision making is not required through the testing process itself (1 point).

Table 3: CLIA Complexity Assessment Access AccuTnI+3 on the UniCel DxC 600i

Category	Access AccuTnI+3 for use on the UniCel DxC 600i
Knowledge	1
Training	1
Reagent Preparation	1
Operational Steps	1
QC/PT Materials Availability/Stability	1
Troubleshooting & Maintenance	1
Judgment	1
Total	**7**
Interpretation	**Moderately complex**

Conclusion: Based on the information provided above Beckman Coulter concludes the AccuTnI+3 on the DxC 600i is CLIA moderately complex category.

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS† WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

†Access 2 and UniCel DxC 600i

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:

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- Symptoms of ischemia;
- New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

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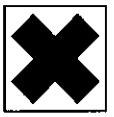
For CLIA Categorization Only

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.



R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.

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- For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
- Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
- If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
- Follow blood collection tube manufacturer's recommendations for centrifugation.
- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for

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information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance of the quality control material. The thermal profile of native human cardiac troponin I was used in development of this assay. Quality control materials containing troponin I not from this source (e.g. recombinant antigens) may behave differently. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (μg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[21,22] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[23,24] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[25] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.

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Records processed under FOIA Request #2013-6265 Released by CDRH on 08-17-2015

7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the

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Records processed under FOIA Request #2013-6265 Released by CDRH on 08-17-2015

diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[26] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 –86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[27] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[28] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

PPV and NPV for Serial Time Intervals
After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[29,30] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[31] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[32] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[33] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[33] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[34]

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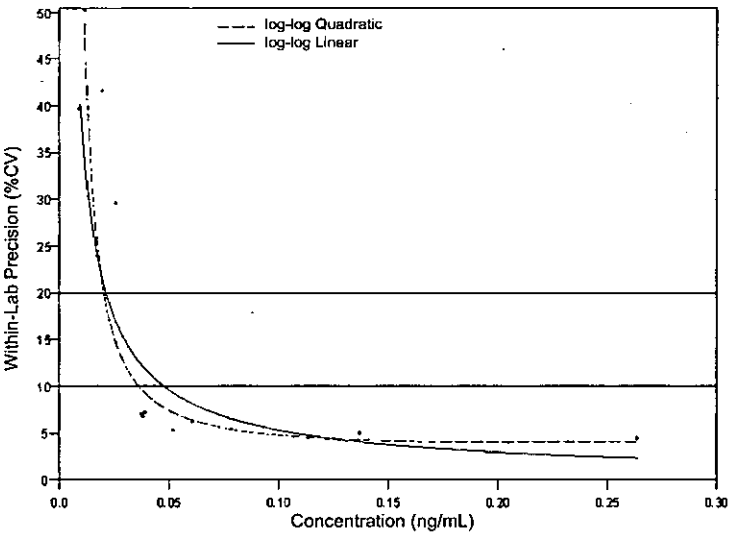
Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[34]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[34] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

Limit of Quantitation (imprecision estimate)



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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510(k) Summary

JUN 1 4 2013

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is k121214

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Date Prepared:

June 12, 2013

Device Name:

Proprietary / Trade Name: Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215
Classification Product Code: MMI

Proprietary / Trade Name: Access AccuTnI+3 Calibrator
Common Name: Calibrator
Classification Name: Calibrator
Classification Regulation: 21 CFR 862.1150
Subsequent Product Code: JIT

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160
Classification Product Code: JJE

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Predicate Devices:

The Access AccuTnI+3 Reagent and AccuTnI+3 Calibrators claim substantial equivalence to the ADVIA Centaur TnI-Ultra™ Assay and ADVIA Centaur TnI-Ultra™ Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Device Description:

The Access AccuTnI+3 reagents, AccuTnI+3 calibrators and the Access 2 Immunoassay System compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI+3 reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

The Access 2 Immunoassay System is an in vitro diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Intended Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

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The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators and the predicate device, ADVIA Centaur® TnI-Ultra™ Assay and ADVIA Centaur® TnI-Ultra™ Calibrators, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Similarities between the Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Access AccuTnI+3Calibrators
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same

Differences between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2 Immunoassay System
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized : high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.02 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.9 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.042 ng/mL	Total CV of ≤8% at concentrations >0.075 ng/mL. SD ≤0.006 at concentrations ≤0.075 ng/mL
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction. The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 System K922823/A007	New Device Access 2 Immunoassay System
Indication for Use	The Access 2 Immunoassay system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

Conclusion: The information provided above demonstrates that the new device, the Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators, have the same intended use as the predicate device. The Access 2 instrument has the same intended use as the predicate device. In addition, verification and validation testing, the clinical and analytical data, the clinical use of the product reflected in current MI diagnostic guidelines, and other scientific information provided in this submission demonstrate that the Access AccuTnI+3 Reagent, Access AccuTnI+3 Calibrators on the Access 2 Immunoassay Systems is as safe and effective as the predicate devices. Taken together, this information establishes the substantial equivalence of Beckman Coulter's products to predicates.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

June 14, 2013

Beckman Coulter, Inc.
C/O Kerrie Oetter
1000 Lake Hazeltine Drive
CHASKA MN 55318-1084

Re: K121214
Trade/Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: II
Product Code: MMI, JIT, JJE
Dated: June 04, 2013
Received: June 06, 2013

Dear Ms. Oetter:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney H. Lias, Ph.D.

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Ruth A. Chesler/S

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k) k121214

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

K121214

Jones, Edwena

From: Caposino, Paula
Sent: Friday, June 14, 2013 10:09 AM
To: 510K Program; Jones, Edwena
Subject: URGENT K121214/S002

Importance: High

Please see the update to the trade name for this device which should be updated in CTS

The sponsor has changed the trade name of this device during the course of the review.
Please update the trade name to:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System.
Thank you.

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This message is automatically generated by JIRA.
-
If you think it was sent incorrectly contact one of the administrators: https://jira-cdrh.fda.gov/jira/secure/Administrators.jspa
-
For more information on JIRA, see: http://www.atlassian.com/software/jira

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

DCC Coversheet for Documents Deleted or Withdrawn from eCopy Hold

Today's Date: 3/26/14

Complete Document Number: K121214/A001

This specific document was not entered into the review queue because:

X It was deleted based on lack of response to the eCopy hold letters(s).

☐ It was withdrawn based on request from the applicant.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

eCopy Hold Letter

May 10, 2013

Valynda Machen, Group Manager, Regulatory Affairs
Beckman Coulter, Inc.
1000 Lake Hazeltine Dr.
Chaska, MN 55318

Dear Valynda Machen:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your submission. This submission has been assigned the following unique document control number below. Failure to reference this assigned number in future correspondence may result in processing delays.

510(k) Number: K121214/A001
Device: Access Accutnl Reagent And Calibrator For Use On The Access 2 Immunoassay Systems
Dated: 09-MAY-2013
Received: 10-MAY-2013

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or flash drive, accompanied by a signed cover letter and the complete original paper submission. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

You have received this letter because you have either not provided an eCopy or you provided an eCopy that failed the loading process because it did not conform to the technical specifications. If you provided an eCopy that failed the loading process, then please see the attached document that identifies all reasons for the failure that need to be addressed.

Please write the specific submission number identified above AND "Replacement eCopy" directly on the CD (or other media) and send that with a paper copy of your cover letter (revised if applicable) to the CDRH Document Control Center (DCC) at the address below.

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

When your Replacement eCopy has been received and been verified as a valid eCopy, review of this submission will start as of that date.

For more information about FDA's new eCopy program, including the new technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf. In addition, we strongly encourage you to visit FDA's eSubmitter website at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm221506.htm in order to develop an eCopy in accordance with the new technical standards prior to sending it to FDA.

If you have any questions concerning this letter, please contact the eCopy Program Coordinators at (240) 402-3717 or at CDRH-eCopyinfo@fda.hhs.gov.

Sincerely yours,

Samie Allen
Policy Analyst
Office of Device Evaluation
Center for Devices and Radiological Health

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Mcdonald, Lisa *

From: Mcdonald, Lisa *
Sent: Friday, May 10, 2013 3:29 PM
To: 'KSOETTER@BECKMAN.COM'
Cc: DCCLetters
Subject: K121214/A001 ECOPY HOLD LETTER (NO ECOPY PROVIDED)
Attachments: K121214.pdf

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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K121214/A001

BECKMAN COULTER®

FDA CDRH DMC

MAY 10 2013

Received

May 09, 2013

Paula Velasco Caposino, Ph.D.
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center-W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-002

RE: 510(k) #k121214 – Official Correspondent
Access AccuTnI+3 on the Access 2 Immunoassay Systems

Dear Dr. Caposino:

The official correspondent for 510(k) #k121214 has changed from Valynda Machen to Kerrie Oetter.

If there are questions, you may contact me by telephone at (952) 368-7858, by fax at (952) 368-7610, or by e-mail at ksoetter@beckman.com.

Sincerely,

Kerrie Oetter
Senior Regulatory Affairs

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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FDA CDRH DMC
JUL 03 2013
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K121214

BECKMAN COULTER

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: CLIA Categorization Request

Dear Madam/Sir:

Beckman Coulter Inc. is submitting the attached documentation to request a CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i system based on 42 CFR 493.15(b) of the CLIA 1988 regulation.

The UniCel DxC 600i system was cleared on February 27, 2006 under k060256. The UniCel DxC 600i system contains an Access 2 Immunoassay System. Under the Reagent Replacement and Instrument Family Policy, the UniCel DxC 600i system is a member of the same instrument family as the Access 2 Immunoassay System. Access AccuTnI+3 on the Access 2 Immunoassay System was cleared by FDA on June 14, 2013 under k121214 and found to be CLIA moderately complex.

A description of the product is provided, in addition to the draft Instructions for Use. The e-copy of this response is an exact duplicate of the paper copy.

Please review this request and contact me if you have any questions.

Sincerely,

Kerrie Oetter
Senior Regulatory Affairs Analyst
Phone: (952) 368-7858
Fax: (952) 3687610
ksoetter@beckman.com

Beckman Coulter, Inc
1000 Lake Hazeltine Drive
Chaska, MN 56318-1084

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: CLIA Categorization Request

Dear Madam/Sir:

Beckman Coulter Inc. is submitting the attached documentation to request a CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i system based on 42 CFR 493.15(b) of the CLIA 1988 regulation.

The UniCel DxC 600i system was cleared on February 27, 2006 under k060256. The UniCel DxC 600i system contains an Access 2 Immunoassay System. Under the Reagent Replacement and Instrument Family Policy, the UniCel DxC 600i system is a member of the same instrument family as the Access 2 Immunoassay System. Access AccuTnI+3 on the Access 2 Immunoassay System was cleared by FDA on June 14, 2013 under k121214 and found to be CLIA moderately complex.

A description of the product is provided, in addition to the draft Instructions for Use. The e-copy of this response is an exact duplicate of the paper copy.

Please review this request and contact me if you have any questions.

Sincerely,

Kerrie Oetter
Senior Regulatory Affairs Analyst
Phone: (952) 368-7858
Fax: (952) 3687610
ksoetter@beckman.com

Beckman Coulter, Inc
1000 Lake Hazeltine Drive
Chaska, MN 56318-1084

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

CLIA complexity categorization for the Access AccuTnI+3 on the UniCel DxC 600i

Product Description:
The Access AccuTnI+3 for Access 2 Immunoassay System (k121214) is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay system to aid in the diagnosis of myocardial infarction. The UniCel DxC 600i (k060256) incorporates an Access 2 system in its platform configuration.

The Access family of immunoassay analyzers consist of microcomputer controlled random and continuous access instruments. The analyzers perform enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction.

Reagent Replacement and Instrument Family:
The Access AccuTnI+3 and the UniCel DxC 600i are eligible for CLIA categorization under the *Guidance for Industry and FDA Staff; Reagent Replacement and Instrument Family Policy* (December 11, 2003). As shown in **Table 1** below, both the instrument and the reagent are 510(k) cleared.

Table 1: Reagent Replacement Regulatory Pathway

Test System Current Regulatory Status		
	Cleared	**New/not cleared**
Reagent	**A – AccuTnI+3 for Access 2 Immunoassay (k121214)**	B
Instrument	**C – UniCel DxC 600i (k060256)**	D

A+C= Replacement Reagent Policy

A summary of the premarket notification 510(k) history for the Access 2 Immunoassay Systems and their respective immunoassay and chemistry analyzer components is provided in **Table 2** below.

Table 2: 510(k) History of the Access® Immunoassay Analyzer Family

Analyzer System	FDA Docket	Clearance Date	Immunoassay Analyzer	Chemistry Analyzer
Access 2 Immunoassay Analyzer Plus AccuTnI+3	K121214	June 14, 2013	Stand-Alone	N/A
UniCel DxC 600i SYNCHRON Access Clinical System	K060256	February 27, 2006	Access 2 Immunoassay Analyzer (Access 2)	UniCel DxC 600 SYNCHRON System analyzer (DxC 600)

CLIA Complexity Evaluation under 42 CFR 493.17(a):
A complexity categorization scoring was performed on the Access AccuTnI+3 for UniCel DxC 600i. The results of the scoring appear in **Table 3**. The categorization was based on the specific criteria outlined in 42 CFR 493.15(b) of the CLIA 1988 regulation. Using those criteria, all seven sections were assigned scores from 1 to 3, with 1 indicating the lowest level of complexity. The Access AccuTnI+3 for UniCel DxC 600i was determined to be moderately complex, having a total score of less than 12 points.

The rating of moderately complex assays is based on the rationale contained in the regulation. For this assay, the analyst needs minimal scientific and technical knowledge beyond the step-by-step directions, which may be obtained through on-the-job instruction, to properly perform the assay procedures and report results (1 point). The analyst needs minimal training and experience for the preanalytic, analytic, and postanalytic phases of the testing process to perform the assay (1 point). The Access AccuTnI+3 for UniCel DxC 600i is liquid, prepackaged, premeasured, and requires no preparation (1 point). The UniCel DxC 600i has automatic specimen processing, computer controlled timing steps, built-in function checks, and no required calculations, necessitating only periodic calibration by the analyst at the request of the software system (1 point). Calibration and control materials are readily available, stable, and easily incorporated into the procedure. Proficiency testing materials are available and stable (1 point). Troubleshooting is clearly described in instrument manuals and maintenance steps can be easily performed with appropriate training (1 point). Minimal interpretation and judgment is required on the part of the analyst as decision making is not required through the testing process itself (1 point).

Table 3: CLIA Complexity Assessment Access AccuTnI+3 on the UniCel DxC 600i

Category	Access AccuTnI+3 for use on the UniCel DxC 600i
Knowledge	1
Training	1
Reagent Preparation	1
Operational Steps	1
QC/PT Materials Availability/Stability	1
Troubleshooting & Maintenance	1
Judgment	1
Total	**7**
Interpretation	**Moderately complex**

Conclusion: Based on the information provided above Beckman Coulter concludes the AccuTnI+3 on the DxC 600i is CLIA moderately complex category.

For CLIA Categorization Only
Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS† WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

†Access 2 and UniCel DxC 600i

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

For CLIA Categorization Only
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- Symptoms of ischemia;
- New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

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R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

   Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.

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- For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
- Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
- If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
- Follow blood collection tube manufacturer's recommendations for centrifugation.
- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for

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information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance of the quality control material. The thermal profile of native human cardiac troponin I was used in development of this assay. Quality control materials containing troponin I not from this source (e.g. recombinant antigens) may behave differently. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[21,22] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[23,24] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[25] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.

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7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the

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diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[26] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 –86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[27] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[28] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[29,30] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[31] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[32] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[33] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[33] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[34]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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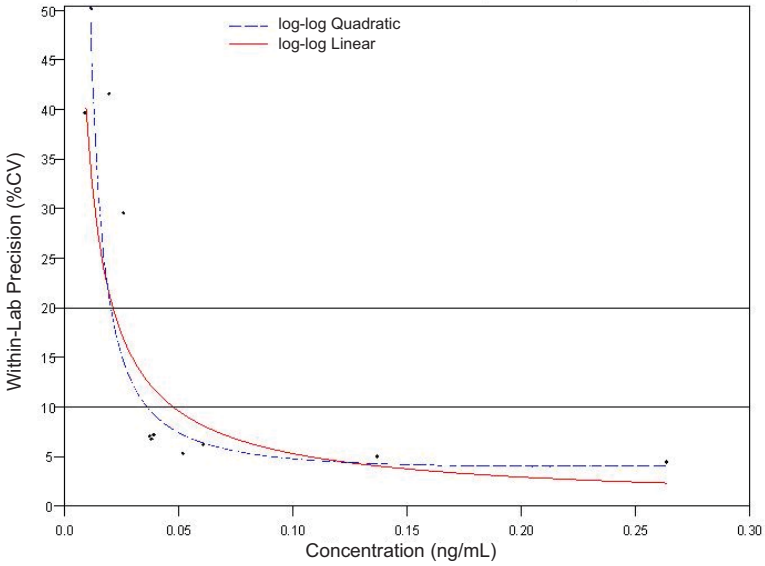
Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[34]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[34] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

Limit of Quantitation (imprecision estimate)



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

June 14, 2013

Beckman Coulter, Inc.
C/O Kerrie Oetter
1000 Lake Hazeltine Drive
CHASKA MN 55318-1084

Re: K121214
Trade/Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: II
Product Code: MMI, JIT, JJE
Dated: June 04, 2013
Received: June 06, 2013

Dear Ms. Oetter:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney H. Lias, Ph.D.

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

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Concurrence & Template History Page

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Tracking Number: K121214

Digital Signature Concurrence Table	
Reviewer Sign-Off	Paula Caposino
Branch Chief Sign-Off	Ruth Chesler
Division Sign-Off	Courtney H. Lias, Ph.D. 2013.06.14 13:02:27 -04'00'

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Sincerely yours,

Courtney H. Lias, Ph.D.

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Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Ruth A. Chesler -S

Division Sign-Off
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510(k) k121214

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Ruth A. Chesler -S

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k) k121214

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
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January 10, 2013

BECKMAN COULTER, INC.
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ATTN: VALYNDA MACHEN

510k Number: K121214
Product: ACCESS ACCUTNL REAGENT AND CAL
On Hold As of 1/8/2013

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

The deficiencies identified represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm.

In accordance with 21 CFR 807.87(l), FDA may consider a 510(k) to be withdrawn if the submitter fails to provide additional information within 30 days of an Additional Information (AI) request. FDA generally permits submitters additional time to respond to such requests. FDA intends to automatically grant a maximum of 180 calendar days from the date of the AI request, even if the submitter has not requested an extension. Therefore, submitters are no longer required to submit written requests for extension. However, submitters should be aware that FDA intends to issue a notice of withdrawal under 21 CFR 807.87(l) if FDA does not receive, in a submission to the appropriate Document Control Center, a complete response to all of the deficiencies in the AI request within 180 calendar days of the date that FDA issued that AI request. In this instance, pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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For further [illegible]s should affect the review clock for purposes of meeting the Medical Device User Fee Amendments of 2012 (MDUFA III), to the Federal Food, Drug, and Cosmetic Act, you may refer to our guidance document entitled "Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals". You may review this document at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm>.

Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Director, 510(k) Program
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Paula Caposino

Subject: 510(k) Number K121214/S001

To: The Record

Please list CTS decision code TH

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☒ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III?			
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)?			
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was			

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conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)

Does this device include an Animal Tissue Source?

All Pediatric Patients age<=21

Neonate/Newborn (Birth to 28 days)

Infant (29 days -< 2 years old)

Child (2 years -< 12 years old)

Adolescent (12 years -< 18 years old)

Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)

Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)

Nanotechnology

Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html) *Contact OC.*

Regulation Number	**Class***	**Product Code**

(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: Carol Bo (Branch Chief) CHTB (Branch Code) 1-8-13 (Date)

Final Review: (Division Director) (Date)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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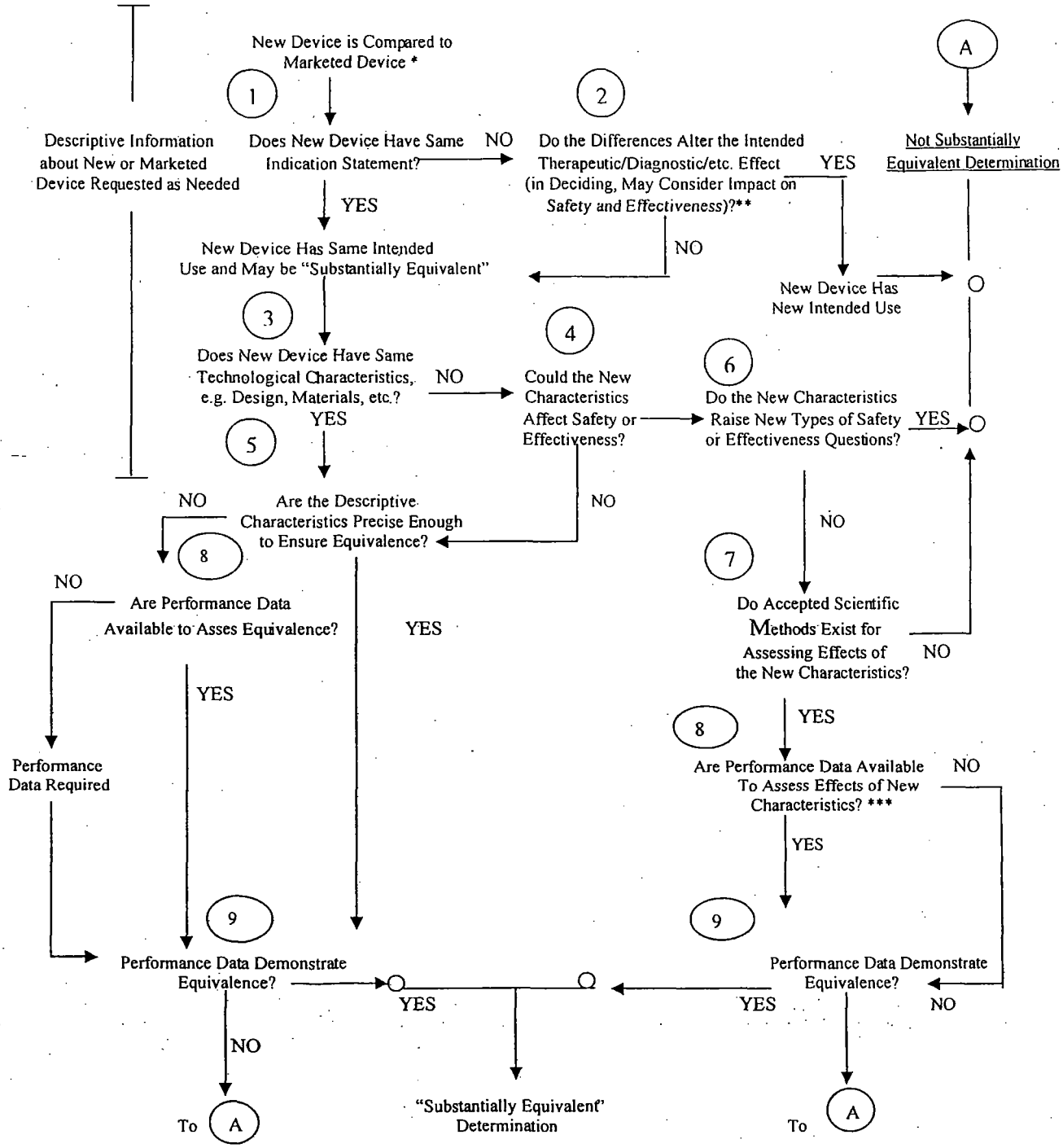
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data may be in the 510(k), other 510(k)s, the Center's classification files, or the literature.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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MEMORANDUM

To: File
From: Paula V. Caposino
RE: k121214/S001
Date: January 8, 2013

Based on discussion with Ian Pilcher (Reviewer DCTD/OIR), Ruth Chesler (Cardio/Renal Branch Chief, DCTD/OIR), Bipasa Biswas (Acting Team Leader of the Diagnostic Devices Branch, DBS/OSB), Kristen Meier (Statistician, DBS/OSB), Carol Benson (Deputy Division Director, DCTD/OIR) my review of the sponsor's response to our letter requesting additional information (dated June 20, 2012) and Chava Zibman's (Mathematical Statistician, DBS/OSB) statistical consult, I recommend that we place k121214/S001 on hold. The items listed below are needed to complete the review of the submission.

1. Thermal sensitivity: In your response to item 1a from our letter requesting additional information dated June 20, 2012, you provided new studies and data from existing studies to demonstrate that your corrective algorithm resolved the temperature sensitivity issue of your device. We have the following concerns with your response:
   a. In the new studies that you performed (and in the data from the low dose samples of the original method comparison study and the pre-verification concordance study), you only evaluated the performance of the device at the temperature extremes. During our October 26, 2012 face-to-face meeting we requested that you evaluate any new data in support of your corrective algorithm at different temperatures spanning the operational temperature range of your device (i.e., not only comparing the performance at the extreme temperatures). However, you only provided data at different temperatures for the concordance analysis for the new concordance study. Therefore, please provide Passing Bablok analyses for all studies in support of your corrective algorithm at different temperatures spanning the operational temperature range of your device (i.e., not only comparing the performance of the device at extreme temperatures). Please make sure that these analyses are performed using singlicate results (in accordance with the intended use of your device). Please provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analyses. You should also provide a table with the proportion of observations above the cut-off at each temperature for FDA review. Please note that for the new concordance study, two thirds of the samples had values above the 0.03 ng/mL cut-off while in the original concordance study that demonstrated unacceptable bias, half of the observations had troponin values above the 0.03 ng/mL cut-off. We are very concerned that the study design for the new concordance studies may not be equivalent to the study design of the original concordance study because the observations in the new studies may have higher troponin values than the original study. You may need to repeat your concordance studies closely mimicking the design of the original concordance study to demonstrate that you have resolved the temperature bias issue.
   b. We are still very concerned about the performance of your device. Specifically, you have not definitively explained the unacceptable bias demonstrated in the original concordance study. You have also not explained why this unacceptable performance will not be

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experienced by the end users of your device and will not affect the safe use of this device on patients. Please note that your discussion about the performance of the existing device without the thermal algorithm on pages 7-9 of your response cannot be used in support of the new device since these devices are not the same. Therefore, we would not anticipate the same performance once the corrective algorithm is implemented.

c. In our October 26, 2012 face-to-face meeting we requested that in your response, you provide the line data from the original concordance study identifying all samples that were acquired from the vendor suspected of not handling the specimens according to your instructions for use. This information was not provided in the response. Please provide this information in support of your hypothesis that sample handling may have caused the unacceptable bias in the original concordance study.

d. In response to deficiencies 1b and 1c, you sought to establish that accuracy is not affected if the device is calibrated at a different temperature than the temperature at which the measurement is made. You reanalyze data by determining what the measurements would have been had a different calibration curve been used. In an email dated December 28, 2012 you clarified that for these studies the calibration curves were generated at the same time as the samples were measured. You concluded that regardless of calibration temperature, the difference in results met the acceptance criteria (slope term of each linear fit is either not significant or significant but has an average slope < 0.010) in all cases. However, it is not clear how it was determined whether or not the slope term of each fit was or was not significant. You should provide this information. We are concerned that a lack of significance may be indicative of an insufficient amount of data rather than a negligible slope. You should provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analyses for FDA review.

2. Limits of Detection: We have the following concerns with your response to deficiency 5:

a. Limit of blank (LoB): In your response to item 5a, you state that "to demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C, we reanalyzed all sample results from the multi-temperature LoB study data using calibration curves generated at 18°C and 28°C." However, in an email dated December 28, 2012 you stated that these calibration curves where not the same calibration curves that were generated at the time the LoB samples were measured. For this reason, we cannot accept the reanalysis in support of your LoB results. Please perform a new LoB study to demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:

- Samples (at least 4 blank samples) calibrated at 18°C and run at 18°C, 23°C, and 28°C
- Same samples calibrated at 23°C and run at 18°C, 23°C, and 28°C
- Same samples calibrated at 28°C and run at 18°C, 23°C, and 28°C

We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline "Protocols for Determination of Limits of Detection and Limits of Quantitation" regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoB study at each calibration temperature for each lot to confirm the results of your standardized LoB study.

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b. Limit of detection (LoD): In your response to item 5b, you also reanalyzed samples from the multi-temperature LoD study using calibration curves generated at 18°C and 28°C. As discussed above, this data does not support your LoD claim because those calibrations were not generated at the same time as the samples were measured. Please perform a new LoD study to demonstrate that the LoD is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:
   - low level patient samples (at least 4) calibrated at 18°C and run at 18°C, 23°C, and 28°C
   - The same low level patient samples calibrated at 23°C and run at 18°C, 23°C, and 28°C
   - The same low level patient samples calibrated at 28°C and run at 18°C, 23°C, and 28°C

   We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoD study at each calibration temperature for each lot to confirm the results of your standardized LoD study.

c. Limit of quantitation (LoQ): In your response to item 5c, you reanalyzed the originally-submitted LoQ data to substantiate the LoQ claim. You concluded that your data supports the claim that your device has a 10% CV LoQ of 0.3 ng/mL and a 20% CV LoQ of 0.02 ng/mL. We do not agree with your conclusion. As discussed above, we cannot use the recalculated data since the calibration curves where not generated at the same time that the samples were measure. Furthermore, you provided data using 7 low level samples on one reagent lot and one instrument which demonstrated that your LoQ is 0.026 with a %CV of 14.2% (data generated at 28°C using instrument 501007). You state that a sample set of 7 is not sufficient to establish an accurate estimate of LoQ. However, each of these 7 samples was measured in 66 replicates. Therefore, it seems that this performance will be experienced by the end user. In order to confirm these results (i.e., LoQ of 0.026 ng/mL with a performance goal of %CV less than 15%), you should provide data from a new LoQ study to demonstrate that the LoQ is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:
   - low level patient samples (at least 4) calibrated at 18°C and run at 18°C, 23°C, and 28°C
   - The same low level patient samples calibrated at 23°C and run at 18°C, 23°C, and 28°C
   - The same low level patient samples calibrated at 28°C and run at 18°C, 23°C, and 28°C

   We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoQ study at each calibration temperature for each lot to confirm your LoQ claim.

   i. If you are able to confirm your LoQ claim, you will not be able to report any values under 0.026 ng/mL troponin (or 0.03 ng/mL depending on the decimal points of the

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reported test results—see question 2cii below) since they are below your LoQ. If this is the case, please reanalyze the data from any study that currently includes data under your LoQ and amend all claims if necessary.

ii. It seems that your instrument may report troponin results using two decimal points. If this is the case, and you can verity your current LoQ, you will need to limit your LoQ claim to 0.03 ng/mL with a performance goal of a %CV of 15%.

3. Linearity: In your response to our request for additional information, you provided data from new linearity studies. However, based on the studies you provided, we cannot determine that your device demonstrates acceptable non linearity at the medical decision point at the different temperatures. The reasons are:
   a. While the lowest sample evaluated was below the LoQ (see item 2c above), the next sample evaluated in the linearity studies contained troponin levels around 10 ng/mL (while the cut-off for the assay is 0.03 ng/mL). Therefore, in order to demonstrate acceptable non-linearity at all temperatures, you will need to provide new studies using patient samples demonstrating the linearity of the device including samples around the cut-off of your device. We recommend that in your new linearity study, you span your claimed range but also include several samples at the lower end of your reportable range (for example a value around your cut-off but above your LoQ and several samples under 1 ng/mL). While we understand that this recommendation deviates from the EP-6 guideline "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach", it is important data that needs to be provided in order to define the linearity of your device including the medical decision point. Please provide a detailed protocol and the results of your new linearity study.
   b. We do not agree with your acceptance criteria for acceptable non linearity. Specifically, based on your current acceptance criteria for values under 0.105 ng/mL, you will allow 56% deviation from non-linearity at the medical decision point (please refer to our discussion below in item 8 regarding your acceptance criteria). We also do not concur with deviation from linearity of ≤ 16% for samples > 0.105 ng/mL. Please limit your measuring range to the range with a deviation from non-linearity of around 10% (but not more than 15%). The reason for this recommendation is that deviation from linearity will add to the total error of this device. Therefore, the large deviation currently accepted, may affect the accuracy of this device and affect its safe use.
   c. To also demonstrate that the linearity of your device is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C, we recommend that you provide data demonstrating acceptable linearity with patient samples run at 18°C, 23°C, and 28°C and calibrated at 18°C, 23°C, and 28°C.

4. Precision: You performed a new precision study using pooled patient samples using 2 reagent lots and 2 instruments at 8 temperatures using calibration curves at 3 temperatures. Please provide the following:
   a. Please provide overall %CV analysis (i.e., incorporation lot to lot, instrument to instrument and temperature to temperature imprecision) for FDA review. This data should be included in the package insert.

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b. Please provide a detailed protocol for the imprecision data currently provided in the labeling (since it does not match any precision data provided in the 510(k)). Please make sure to provide overall % CV results (incorporating lot to lot, instrument to instrument, temperature to temperature, etc., imprecision) for FDA review and in your package insert.

5. Field Effectiveness Studies: Please provide the following information regarding your external field effectiveness studies:
   a. Please provide the thermal bias before and after the application of the thermal algorithm for the external field effectiveness studies.
   b. Please confirm that all QC samples used in the external field effectiveness studies also reflect the thermal behavior of natural patient samples. If not, you will need to repeat these studies preferably using unmodified patient samples at relevant troponin concentrations (i.e., around the 0.03 ng/mL cut-off of the device). Please note that FDA still does not agree with your acceptance criteria for concentration > 0.105 ng/mL of ≤ 0.0084 SD since at the medical decision point you are claiming this translates to ± 28% change (refer to item 8 for additional discussion regarding your acceptance criteria). If you need to repeat your studies, please tighten your acceptance criteria based on acceptable clinical performance around the new cut-off of your new device. Please provide a detailed protocol of your new studies, results of your new studies including the recorded ambient temperatures of the laboratories during the testing.

6. Matrix Comparison: In order to support that your device can be used using serum samples, you provided Deming regression analysis and Bland-Altman plots from 107 matched serum and plasma samples. You also provided a concordance analysis and ROC characteristic curves for plasma vs. serum samples based on the 0.03 ng/mL cut-off. We have the following concerns with your approach.
   a. Since your LoQ seems to be 0.03 ng/mL (which is also your medical decision point) you need to exclude samples with values below the LoQ from your Deming regression analysis. This creates a problem for us because we cannot evaluate the quantitative performance of your assay for serum and plasma samples with troponin values below 0.03 ng/mL. Based on the line data from your clinical study, there are 3575 measurements out of a total of 4596 measurements that are below your LoQ (this is about 78% of the results from your clinical study). Therefore, we believe that you need to demonstrate the clinical performance of this device using serum samples. While you provided concordance analysis and ROC analysis comparing plasma and serum samples, it seems that this data is biased since 61% of these samples have a final MI diagnosis compared to around 13% of plasma samples in your clinical study with a final MI diagnosis. Therefore, we still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) using serum samples.

7. Pivotal Clinical trial: In response to deficiency 3cii, you stated that adjusting for repeated measures is not appropriate (and for this reason you only use one observation per person per time period) due to the way troponin measures are taken in practice. Please provide a table with all troponin test results from any patient that had multiple draws in a given bin for FDA review.

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8. Acceptance criteria: As we have discussed in several sections above, we do not agree with the acceptance criterion of 0.0084 SD for troponin values under 0.105 ng/mL. While you developed this acceptance criterion based on the decision point of the current assay (i.e., 0.06 ng/mL), since the decision point for the new assay has changed, FDA believes that the acceptance criterion developed for the current assay are not appropriate for the new assay with the new and lower claimed cut-off. For the proposed device with the current cut-off, this criterion seems to translates to ± 28%. Please tighten these criteria to address your new device and your new cut-off. Please amend all necessary claims and update your labeling accordingly.

9. Stability: We have reviewed the stability data provided in support of your stability claims. We have the following concerns:
   a. Reagent real time stability and calibrator real time stability: We are still very concerned that the acceptance criteria for allowable change in your stability studies are too broad for the intended use of this device. Specifically, we are concerned that the Z value uses the observed dose in the calculation and therefore depends on the performance of the device. The acceptance criteria needs to be based on a fixed acceptable change in the performance of the device designed based on the medical needs of the device (e.g., allowable drift of ± 10%). We also disagree with the acceptance criteria that all replicates should be within 3SD (of the expected SD). We are concerned that this is too broad for the intended use of this device. Please narrow your criteria and amend your stability claims. You need to design your acceptance criteria to ensure that a test result is the same at the end of the claimed stability interval compared to the value obtained at baseline. Please provide your reagent and calibrator real time stability data in the same format as you have provided the open pack stability, calibration stability and calibrator open vial stability data to demonstrate acceptable stability in relation to % from baseline (including all individual replicates).
   b. Reagent open pack, calibration stability and open vial calibrator stability: While it seems that the majority of the replicates in your reagent open pack, calibration stability and calibrator open vial stability studies demonstrate acceptable drift (generally within ± 10% from baseline), we are concerned that the acceptance criteria are too broad for the intent of this testing. As discussed above for reagent real time stability, we recommend that you narrow your criterion (e.g., allowable drift of ± 10%) and amend your claims if necessary. You need to design your acceptance criteria to ensure that a test result is the same at the end of the claimed stability interval compared to a value at baseline.

10. Calibrators: You provided additional information about the value assignment process for the calibrators. You state that the acceptance criteria for value assignment is SD ≤ 0.0084 for S1 (the 0 calibrator) and 8% for S2 to S6. You provided a table with data for 3 calibrator lots. You state that doses generated from pre-specified RLU's that are < 0.04 ng/mL are not used for evaluation. Please explain why you do not evaluate doses less than 0.04 ng/mL (which is above your medical decision cut-off). It seems that doses above your LoQ need to be evaluated. You list the following reference doses (lot 117302 as an example) in table I; 0.044, 0.626, 0.13, 0.21, 0.28, 0.31, 0.66, 1.00, 1.34, 1.69, 2.37, 3.05, 3.73, 4.76, 6.14, 7.54, 10.39, 14.05, 17.84, 21.77, 25.85, 30.10, 39.16 and 65.76. It is not clear what these results

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are (i.e., what was measured, calibrators, quality control samples, patient samples, etc.). Please explain what these results are and how they are substantiating the assigned value of your kit calibrators. Please provide more information about the acceptance criteria for calibrator value assignment. For example, which assay results need to be within 0.0084SD and which results need to be within 8%. Please refer to item 8 for discussion regarding our concern with your acceptance criteria. We do not believe that an allowable drift of 28% around the medical decision point of this assay is appropriate for its calibrators. Also, you state that dose values for commercial calibrators must fall within quality control ranges. Please specify these ranges for each calibrator and discuss why you believe they are appropriate for the intended use of this device. Please specify how your procedure controls drift in the assigned value of the kit calibrators in subsequent calibrator lots.

11. Labeling: Please amend your claims based on the recommendation above. Also, please address the following:
    a. Please include the sensitivity, specificity, positive predictive value and negative predictive value performance of your device for the ≥ 6-9 hour time interval.
    b. Since your corrective algorithm was designed to reduce the thermal sensitivity from around 3.5% to <1% per degree, we recommend that you include this information in the package insert.

12. Please submit a new intended use form and 510(k) summary with your response (if necessary).

Reviewer Name and Signature:

Paula V. Caposino

Paula Velasco Caposino, Ph.D.
FDA/CDRH/OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Caposino, Paula
Sent: Tuesday, January 08, 2013 5:20 PM
To: 'Machen, Valynda (Valynda) L'
Subject: k121214-S001

Re: k121214/S001
Trade Name: Access AccuTnI+3 on the Access 2 Immunoassay Systems
Dated: December 14, 2012
Received: December 17, 2012

Dear Valynda Machen:

Thank you for your response. We have reviewed the additional information that you provided. However, we cannot determine if the device is substantially equivalent to a legally marketed predicate device because your responses to the deficiencies in our June 20, 2012 letter raised new issues. In order to complete the review of your submission, we require additional information. Therefore I am putting your submission on hold pending receipt of this information. This email is your formal notification of the hold and takes the place of the "Request for Additional Information" letter. If you need more than 30 days to respond to this email, please follow the same procedure to ask for an extension from the Document Mail Center as you would with the formal "Request for Additional Information" letter.

Please send the requested information to me electronically so I can check it for completeness first. If all of the information is in order, I will then ask you to send it in to the Document Mail Center.

1. Thermal sensitivity: In your response to item 1a from our letter requesting additional information dated June 20, 2012, you provided new studies and data from existing studies to demonstrate that your corrective algorithm resolved the temperature sensitivity issue of your device. We have the following concerns with your response:
   a. In the new studies that you performed (and in the data from the low dose samples of the original method comparison study and the pre-verification concordance study), you only evaluated the performance of the device at the temperature extremes. During our October 26, 2012 face-to-face meeting we requested that you evaluate any new data in support of your corrective algorithm at different temperatures spanning the operational temperature range of your device (i.e., not only comparing the performance at the extreme temperatures). However, you only provided data at different temperatures for the concordance analysis for the new concordance study. Therefore, please provide Passing Bablok analyses for all studies in support of your corrective algorithm at different temperatures spanning the operational temperature range of your device (i.e., not only comparing the performance of the device at extreme temperatures). Please make sure that these analyses are performed using singlicate results (in accordance with the intended use of your device). Please provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analyses. You should also provide a table with the proportion of observations above the cut-off at each temperature for FDA review. Please note that for the new concordance study, two thirds of the samples had values above the 0.03 ng/mL cut-off while in the original concordance study that demonstrated unacceptable bias, half of the observations had troponin values above the 0.03 ng/mL cut-off. We are very concerned that the study design for the new concordance studies may not be equivalent to the study design of the original concordance study because the observations in the new studies may have higher troponin values than the original

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study. You may need to repeat your concordance studies closely mimicking the design of the original concordance study to demonstrate that you have resolved the temperature bias issue.

b. We are still very concerned about the performance of your device. Specifically, you have not definitively explained the unacceptable bias demonstrated in the original concordance study. You have also not explained why this unacceptable performance will not be experienced by the end users of your device and will not affect the safe use of this device on patients. Please note that your discussion about the performance of the existing device without the thermal algorithm on pages 7-9 of your response cannot be used in support of the new device since these devices are not the same. Therefore, we would not anticipate the same performance once the corrective algorithm is implemented.

c. In our October 26, 2012 face-to-face meeting we requested that in your response, you provide the line data from the original concordance study identifying all samples that were acquired from the vendor suspected of not handling the specimens according to your instructions for use. This information was not provided in the response. Please provide this information in support of your hypothesis that sample handling may have caused the unacceptable bias in the original concordance study.

d. In response to deficiencies 1b and 1c, you sought to establish that accuracy is not affected if the device is calibrated at a different temperature than the temperature at which the measurement is made. You reanalyze data by determining what the measurements would have been had a different calibration curve been used. In an email dated December 28, 2012 you clarified that for these studies the calibration curves were generated at the same time as the samples were measured. You concluded that regardless of calibration temperature, the difference in results met the acceptance criteria (slope term of each linear fit is either not significant or significant but has an average slope < 0.010) in all cases. However, it is not clear how it was determined whether or not the slope term of each fit was or was not significant. You should provide this information. We are concerned that a lack of significance may be indicative of an insufficient amount of data rather than a negligible slope. You should provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analyses for FDA review.

2. Limits of Detection: We have the following concerns with your response to deficiency 5:

a. Limit of blank (LoB): In your response to item 5a, you state that "to demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C, we reanalyzed all sample results from the multi-temperature LoB study data using calibration curves generated at 18°C and 28°C." However, in an email dated December 28, 2012 you stated that these calibration curves where not the same calibration curves that were generated at the time the LoB samples were measured. For this reason, we cannot accept the reanalysis in support of your LoB results. Please perform a new LoB study to demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:

- Samples (at least 4 blank samples) calibrated at 18°C and run at 18°C, 23°C, and 28°C
- Same samples calibrated at 23°C and run at 18°C, 23°C, and 28°C
- Same samples calibrated at 28°C and run at 18°C, 23°C, and 28°C

We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline "Protocols for Determination of Limits of Detection and Limits of Quantitation" regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoB study at each calibration temperature for each lot to confirm the results of your standardized LoB study.

b. Limit of detection (LoD): In your response to item 5b, you also reanalyzed samples from the multi-temperature LoD study using calibration curves generated at 18°C and 28°C. As discussed above, this data does not support your LoD claim because those calibrations were not generated at the same time as the samples were measured. Please perform a new LoD study to demonstrate that the LoD is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:

- low level patient samples (at least 4) calibrated at 18°C and run at 18°C, 23°C, and 28°C

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- The same low level patient samples calibrated at 23°C and run at 18°C, 23°C, and 28°C
- The same low level patient samples calibrated at 28°C and run at 18°C, 23°C, and 28°C

We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoD study at each calibration temperature for each lot to confirm the results of your standardized LoD study.

c. Limit of quantitation (LoQ): In your response to item 5c, you reanalyzed the originally-submitted LoQ data to substantiate the LoQ claim. You concluded that your data supports the claim that your device has a 10% CV LoQ of 0.3 ng/mL and a 20% CV LoQ of 0.02 ng/mL. We do not agree with your conclusion. As discussed above, we cannot use the recalculated data since the calibration curves where not generated at the same time that the samples were measure. Furthermore, you provided data using 7 low level samples on one reagent lot and one instrument which demonstrated that your LoQ is 0.026 with a %CV of 14.2% (data generated at 28°C using instrument 501007). You state that a sample set of 7 is not sufficient to establish an accurate estimate of LoQ. However, each of these 7 samples was measured in 66 replicates. Therefore, it seems that this performance will be experienced by the end user. In order to confirm these results (i.e., LoQ of 0.026 ng/mL with a performance goal of %CV less than 15%), you should provide data from a new LoQ study to demonstrate that the LoQ is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:
   - low level patient samples (at least 4) calibrated at 18°C and run at 18°C, 23°C, and 28°C
   - The same low level patient samples calibrated at 23°C and run at 18°C, 23°C, and 28°C
   - The same low level patient samples calibrated at 28°C and run at 18°C, 23°C, and 28°C

   We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoQ study at each calibration temperature for each lot to confirm your LoQ claim.
   i. If you are able to confirm your LoQ claim, you will not be able to report any values under 0.026 ng/mL troponin (or 0.03 ng/mL depending on the decimal points of the reported test results—see question 2cii below) since they are below your LoQ. If this is the case, please reanalyze the data from any study that currently includes data under your LoQ and amend all claims if necessary.
   ii. It seems that your instrument may report troponin results using two decimal points. If this is the case, and you can verity your current LoQ, you will need to limit your LoQ claim to 0.03 ng/mL with a performance goal of a %CV of 15%.

3. Linearity: In your response to our request for additional information, you provided data from new linearity studies. However, based on the studies you provided, we cannot determine that your device demonstrates acceptable non linearity at the medical decision point at the different temperatures. The reasons are:
   a. While the lowest sample evaluated was below the LoQ (see item 2c above), the next sample evaluated in the linearity studies contained troponin levels around 10 ng/mL (while the cut-off for the assay is 0.03 ng/mL). Therefore, in order to demonstrate acceptable non-linearity at all temperatures, you will need to provide new studies using patient samples demonstrating the linearity of the device including samples around the cut-off of your device. We recommend that in your new linearity study, you span your claimed range but also include several samples at the lower end of your reportable range (for example a value around your cut-off but above your LoQ and several samples under 1 ng/mL). While we understand that this recommendation deviates from the EP-6 guideline "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach", it is important data that needs to be provided in order to define the linearity of your device including the medical decision point. Please provide a detailed protocol and the results of your new linearity study.
   b. We do not agree with your acceptance criteria for acceptable non linearity. Specifically, based on your current acceptance criteria for values under 0.105 ng/mL, you will allow 56% deviation from non-

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linearity at the medical decision point (please refer to our discussion below in item 8 regarding your acceptance criteria). We also do not concur with deviation from linearity of ≤ 16% for samples > 0.105 ng/mL. Please limit your measuring range to the range with a deviation from non-linearity of around 10 (but not more than 15%). The reason for this recommendation is that deviation from linearity will add to the total error of this device. Therefore, the large deviation currently accepted, may affect the accuracy of this device and affect its safe use.

c. To also demonstrate that the linearity of your device is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C, we recommend that you provide data demonstrating acceptable linearity with patient samples run at 18°C, 23°C, and 28°C and calibrated at 18°C, 23°C, and 28°C.

4. Precision: You performed a new precision study using pooled patient samples using 2 reagent lots and 2 instruments at 8 temperatures using calibration curves at 3 temperatures. Please provide the following:
   a. Please provide overall %CV analysis (i.e., incorporation lot to lot, instrument to instrument and temperature to temperature imprecision) for FDA review. This data should be included in the package insert.
   b. Please provide a detailed protocol for the imprecision data currently provided in the labeling (since it does not match any precision data provided in the 510(k)). Please make sure to provide overall % CV results (incorporating lot to lot, instrument to instrument, temperature to temperature, etc., imprecision) for FDA review and in your package insert.

5. Field Effectiveness Studies: Please provide the following information regarding your external field effectiveness studies:
   a. Please provide the thermal bias before and after the application of the thermal algorithm for the external field effectiveness studies.
   b. Please confirm that all QC samples used in the external field effectiveness studies also reflect the thermal behavior of natural patient samples. If not, you will need to repeat these studies preferably using unmodified patient samples at relevant troponin concentrations (i.e., around the 0.03 ng/mL cut-off of the device). Please note that FDA still does not agree with your acceptance criteria for concentration > 0.105 ng/mL of ≤ 0.0084 SD since at the medical decision point you are claiming this translates to ± 28% change (refer to item 8 for additional discussion regarding your acceptance criteria). If you need to repeat your studies, please tighten your acceptance criteria based on acceptable clinical performance around the new cut-off of your new device. Please provide a detailed protocol of your new studies, results of your new studies including the recorded ambient temperatures of the laboratories during the testing.

6. Matrix Comparison: In order to support that your device can be used using serum samples, you provided Deming regression analysis and Bland-Altman plots from 107 matched serum and plasma samples. You also provided a concordance analysis and ROC characteristic curves for plasma vs. serum samples based on the 0.03 ng/mL cut-off. We have the following concerns with your approach.
   a. Since your LoQ seems to be 0.03 ng/mL (which is also your medical decision point) you need to exclude samples with values below the LoQ from your Deming regression analysis. This creates a problem for us because we cannot evaluate the quantitative performance of your assay for serum and plasma samples with troponin values below 0.03 ng/mL. Based on the line data from your clinical study there are 3575 measurements out of a total of 4596 measurements that are below your LoQ (this is about 78% of the results from your clinical study). Therefore, we believe that you need to demonstrate the clinical performance of this device using serum samples. While you provided concordance analysis and ROC analysis comparing plasma and serum samples, it seems that this data is biased since 61% of these samples have a final MI diagnosis compared to around 13% of plasma samples in your clinical study with a final MI diagnosis. Therefore, we still recommend that you evaluate the serum samples from

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your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity negative predictive value and positive predictive value) using serum samples.

7. Pivotal Clinical trial: In response to deficiency 3cii, you stated that adjusting for repeated measures is not appropriate (and for this reason you only use one observation per person per time period) due to the way troponin measures are taken in practice. Please provide a table with all troponin test results from any patient that had multiple draws in a given bin for FDA review.

8. Acceptance criteria: As we have discussed in several sections above, we do not agree with the acceptance criterion of 0.0084 SD for troponin values under 0.105 ng/mL. While you developed this acceptance criterion based on the decision point of the current assay (i.e., 0.06 ng/mL), since the decision point for the new assay has changed, FDA believes that the acceptance criterion developed for the current assay are not appropriate for the new assay with the new and lower claimed cut-off. For the proposed device with the current cut-off, this criterion seems to translates to ± 28%. Please tighten these criteria to address your new device and your new cut-off. Please amend all necessary claims and update your labeling accordingly.

9. Stability: We have reviewed the stability data provided in support of your stability claims. We have the following concerns:
   a. Reagent real time stability and calibrator real time stability: We are still very concerned that the acceptance criteria for allowable change in your stability studies are too broad for the intended use of this device. Specifically, we are concerned that the Z value uses the observed dose in the calculation and therefore depends on the performance of the device. The acceptance criteria needs to be based on a fixed acceptable change in the performance of the device designed based on the medical needs of the device (e.g., allowable drift of ± 10%). We also disagree with the acceptance criteria that all replicates should be within 3SD (of the expected SD). We are concerned that this is too broad for the intended use of this device. Please narrow your criteria and amend your stability claims. You need to design your acceptance criteria to ensure that a test result is the same at the end of the claimed stability interval compared to the value obtained at baseline. Please provide your reagent and calibrator real time stability data in the same format as you have provided the open pack stability, calibration stability and calibrator open vial stability data to demonstrate acceptable stability in relation to % from baseline (including all individual replicates).
   b. Reagent open pack, calibration stability and open vial calibrator stability: While it seems that the majority of the replicates in your reagent open pack, calibration stability and calibrator open vial stability studies demonstrate acceptable drift (generally within ± 10% from baseline), we are concerned that the acceptance criteria are too broad for the intent of this testing. As discussed above for reagent real time stability, we recommend that you narrow your criterion (e.g., allowable drift of ± 10%) and amend your claims if necessary. You need to design your acceptance criteria to ensure that a test result is the same at the end of the claimed stability interval compared to a value at baseline.

10. Calibrators: You provided additional information about the value assignment process for the calibrators. You state that the acceptance criteria for value assignment is SD ≤ 0.0084 for S1 (the 0 calibrator) and 8% for S2 to S6. You provided a table with data for 3 calibrator lots. You state that doses generated from pre-specified RLU's that are < 0.04 ng/mL are not used for evaluation. Please explain why you do not evaluate doses less than 0.04 ng/mL (which is above your medical decision cut-off). It seems that doses above your LoQ need to be evaluated. You list the following reference doses (lot 117302 as an example) in table I; 0.044, 0.626, 0.13, 0.21, 0.28, 0.31, 0.66, 1.00, 1.34, 1.69, 2.37, 3.05, 3.73, 4.76, 6.14, 7.54, 10.39, 14.05, 17.84, 21.77, 25.85, 30.10, 39.16 and 65.76. It is not clear what these results are (i.e., what was measured, calibrators, quality control samples, patient samples, etc.). Please explain what these results are and how they are substantiating the assigned value of your kit calibrators. Please provide more information about the acceptance criteria for calibrator value assignment. For example, which assay results need to be within 0.0084SD and which results need to be within 8%. Please refer to item 8 for discussion

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regarding our concern with your acceptance criteria. We do not believe that an allowable drift of 28% around the medical decision point of this assay is appropriate for its calibrators. Also, you state that dose values for commercial calibrators must fall within quality control ranges. Please specify these ranges for each calibrator and discuss why you believe they are appropriate for the intended use of this device. Please specify how your procedure controls drift in the assigned value of the kit calibrators in subsequent calibrator lots.

11. Labeling: Please amend your claims based on the recommendation above. Also, please address the following:
    a. Please include the sensitivity, specificity, positive predictive value and negative predictive value performance of your device for the ≥ 6-9 hour time interval.
    b. Since your corrective algorithm was designed to reduce the thermal sensitivity from around 3.5% to <1 per degree, we recommend that you include this information in the package insert.

12. Please submit a new intended use form and 510(k) summary with your response (if necessary).

Once we receive your response to the above deficiencies regarding your 510(k) submission, please be advised that there may be additional issues that arise after further review of your submission.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act (Act) for determining substantial equivalence of your device.

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Act. You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations (21 CFR 812).

In accordance with 21 CFR 807.87(l), FDA may consider a 510(k) to be withdrawn if the submitter fails to provide additional information within 30 days of an Additional Information (AI) request. FDA generally permits submitters additional time to respond to such requests. FDA intends to automatically grant a maximum of 180 calendar days from the date of the AI request, even if the submitter has not requested an extension. Therefore, submitters are no longer required to submit written requests for extension. However, you should be aware that FDA intends to issue a notice of withdrawal under 21 CFR 807.87(l) if FDA does not receive, in a submission to the appropriate Document Control Center, a complete response to all of the deficiencies in this AI request within 180 calendar days of the date of this request. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

For further information regarding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee Amendments of 2012 (MDUFA III), to the Federal Food, Drug, and Cosmetic Act, you may refer to our guidance document entitled "Guidance for Industry and Food and Drug Administration Staff FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals". You may review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm. The requested information should reference your above 510(k) number and should be submitted in duplicate to:

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If you have any questions concerning the contents of the letter and would like to set up a teleconference, please contact me. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100, or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm

Sincerely yours,

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Caposino, Paula

From: Zibman, Chava
Sent: Thursday, January 03, 2013 11:18 PM
To: Caposino, Paula
Cc: Biswas, Bipasa
Subject: RE: K121214/S001
Attachments: CZ_review_K121214 Jan2013.doc

Attached are my comments on the 510K. I wish I could done more, especially regarding the non-clinical studies. As far as the thermal sensitivity issues go, I think it comes down to whether or not you believe their explanation for why the previous data were so underwhelming. I'd be happy to discuss further when I get back to work.

Chava

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Date: January 4, 2032

From: Chava Zibman, PhD (Mathematical Statistician)

DBS/OSB/CDRH

Subject: Statistical Review for K121214, Access TnI on the Access 2 Immunoassay System, by Beckman Coulter

To: Paula Caposino

DCTD/OIVD/CDRH

Background

This is a statistical review of K121214 regarding the Access TnI assay (for Troponin) by Beckman Coulter. Pre-IDE I100255 was first submitted for the pivotal study of this assay in March 2010. No IDE was submitted. A major concern regarding this device is that its performance changes according to the temperature of the room in which the assay in analyzed. I first reviewed this submission in June 2012. This memo is concerned with the sponsor's latest response to FDA feedback. I focused on issues raised in questions 1, 3, and 5.

Indications for use

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

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Item 1: Thermal Sensitivity
1a
In the initial submission, a thermal sensitivity study was performed in which samples were either tested at 18, 22, and 26°C or 20, 24, and 28°C. In this study, higher temperatures consistently yielded higher troponin measurements.nnFor example, the slope in the Passing-Bablok regression comparing measurements taken at 20 and 28 degrees was 1.46 with a 95% confidence interval of (1.36, 1.54). For measurements taken in 18 and 26°C the slope was 1.33 with a 95% confidence interval of (1.26, 1.40). After performing a root cause analysis, the sponsor states in the current submission that "the unacceptable slopes calculated from the Concordance Study data resulted not from a faulty thermal algorithm, but from a set of samples that behaved differently from sample sets used in all other studies." They believe that samples in the original study may not have been handled correctly.

The sponsor performed a new concordance study and obtained much more favorable results than were obtained in the previous submission. The sponsor obtained the following results:

Table 1-5: Concordance Study - Passing-Bablok Regression and Pearson Correlation

Comparison	N	R^2	P-B Slope	Slope 95% CI
18 °C vs. 26 °C	110	1.00	0.96	0.93 – 0.98
20 °C vs. 28 °C	110	0.99	0.98	0.95 – 1.00

Comments: I verified the sponsor's Passing-Bablok results. What should have been included is that the intercepts in both cases were estimated at zero with 95% CIs of [0,0]. I defer to OIR as to whether the sponsor's explanation of sample mishandling is a plausible explanation for the original failed concordance study. The sponsor should explain why conditions that are similarly likely to result in inaccurate measurements cannot be expected to occur during regular use of the device.

I obtain the following results not provided by the sponsor.

Comparison	P-B slope	Slope 95% CI	P-B Intercept	P-B Intercept CI	Average difference	Std Dev difference
18 °C vs. 22 °C	0.99	(0.97,1.00)	0.00	(0.00, 0.00)	.0128333	.1494974
18 °C vs. 26 °C	0.96	(0.93, 0.98)	0.00	(0.00, 0.00)	-.00225	.0197324
22 °C vs. 26 °C	0.96	(0.94,0.99)	0.00	(0.00, 0.00)	-.0150833	.1491652
20 °C vs. 24 °C	1.01	(1.00, 1.03)	0.00	(0.00, 0.00)	.0037182	.0081984
20 °C vs. 28 °C	0.98	(0.95 ,1.00)	0.00	(0.00, 0.00)	.0008182	.0110439
24 °C vs. 28 °C	0.97	(0.95, 0.97)	0.00	(0.00, 0.00)	-.0029	.0115305

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The sponsor provided results of other concordance studies including a preverification concordance study and several .
In the original concordance study (that I reviewed in June 2012), roughly half the observations were above the cutoff of 0.03. In the new study, roughly two-thirds of the observations are above this cutoff and approximately 55% are above 0.06 ng/ml. Out of 110 observations, 6 (5.5%) were discordant at 18 and 26 degrees. That is, 5 were below the cutoff at 18 degrees and above the cutoff at 26 degrees. A single observations was above the cutoff at 18 and below at 26.

Six observations were different at 22 and 26 degrees. All were positive at 22 and negative at 26.

Four were discordant between 18 and 22 degrees. Three were positive at 18 and negative at 22. 1 was negative at 18 and positive at 22.

Out of 110 (different dataset) observations tested at 20 and 28 degrees, three were below the cutoff at 20 and above the cutoff at 28.

Only one observation was discordant between 28 (positive) and 24 (negative) degrees. Two observations that were positive at 24 were negative at 20.

To answer Paula's question, I looked to see whether an increase or decrease of 10% from the 20 degree and 22 degree data would change whether a troponin value was above or below the 0.03 ng/ml cutoff. This was an issue for 4/110 of the 20 degree samples and 3/108 of the 22 degree samples. In all cases, the unadjusted estimate was above the cutoff but would be below the cutoff if decreased by 10%.

1b and 1c
The sponsor sought to establish that accuracy is not affected if the device is calibrated at a different temperature than the temperature at which the measurement is made. They were able to reanalyze data by determining what the measurements would have been had a different calibration curve been used.

The sponsor concludes that:

> Regardless of calibration temperature, the difference in results meets the acceptance criteria (slope term of each linear fit is either not significant or significant but has an average slope < 0.010) in all cases

Comments: The sponsor should provide the raw data corresponding to this analysis. In any case, it is not clear how it was determined whether or not the slope term of each fit was or was not significant. Confidence intervals for all slope estimates should be provided. In addition, the sponsor should realize that lack of significance may be indicative of an insufficient amount of data rather than a negligible slope. The sponsor should similarly provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analysis provided. These were not provided for the results presented on pages 28 and 29 of the submission.

Item 3: Pivotal Trial
The sponsor clarified that, for the purpose of the AUC analysis, if a subject was tested twice in a given time interval, only the second draw was used in calculated the AUC. They

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claim that, in practice, a second test generally means that the first was not valid and thus the second is more likely to have been relied upon clinically. The same logic was used for the poolability analysis. The sponsor clarified how they tested for heterogeneity by site as regarded the AUC. The sponsor also provided information on the proportion of subjects with MI by site. The sponsor declined to provide further performance data by site claiming that it would not be statistically significant.

Comment: I did not ask for by-site data because I thought it would be significant but rather because I believe there had been some concern (I do not remember exactly) about case mix and variation in performance by hospital. I do not believe that the lack of this data is important right now, though I wish the sponsor had provided it. I disagree that small sample size by group is a reason not to provide the numbers that are available. The sponsor's claim that "a minimum of 73 MI's are required to assess cutoffs at 95% sensitivity, and 139 MI's are required to assess cutoffs at 90% sensitivity " ***does not make sense.***

The sponsor claims further that adjusting for repeated measures is not appropriate (and for this reason they only use one observation per person per time period) due to the way troponin measures are taken in practice. I will need to discuss this matter with a clinician to understand it further. That said, if OIR is comfortable with the sponsor's justification for only using the last observation per person per time period, I do not think the issue is worth pressing further at this time.

The sponsor provided data on sensitivity and specificity by time period by cutoff. The sponsor also clarified how observations were binned by time period. As requested, the sponsor repeated confidence interval calculations using the exact rather than the Wald method. The sponsor provided clarification regarding their inclusion criteria and calibration methods.

Item 5: Limit of Detection and other analytical studies

FDA had asked the sponsor to repeat their limit of blank (LoB) and limit of detection (LoD) studies since these studies were not performed under the calibration conditions that the device will be used in practice. The sponsor countered that they are able to estimate what the measurements would have been had the device been calibrated differently and that no new studies are needed.

FDA was concerned that the LoQ (already very close to the 0.03 cutoff) is affected by changes in temperature.

Comment: As I understand it, the sponsor claims that their results are different from those of FDA's because of how data are pooled across instruments. OIR should consider what pooling is appropriate but in studies such as this one the lack of pooling can just as easily increase the LoQ as decrease it. If FDA does not believe pooling is appropriate, I believe the best strategy is to take the worst case out of each set of studies. While the appropriate cutoff in an LoQ study is also a qualitative judgment call, it seems that the cutoff should not be equal to the cutoff for positive and negative diagnoses of MI. If the 20% LoQ is 0.011 ng/ml at 18 degrees and 0.024 ng/ml at 26 degrees (see the

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sponsor's table 5-3), it seems that there is some variation. What level of variation is acceptable, I cannot tell you.

If you have any questions about this review, please contact me at (301) 796-5325 or at

chava.zibman@fda.hhs.gov.

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Friday, December 28, 2012 12:52 PM
To: Caposino, Paula
Cc: Machen, Valynda (Valynda) L
Subject: K121214/S001

Hello Paula,

In total, results were recalculated against alternative calibration curves for six different studies to respond to the 510k deficiencies outlined by the agency. For three such studies the alternate calibration curves were in deed part of the original study design and were generated at the same time as the samples were measured. The studies include Thermal Sensitivity - Robustness (Table 1-10), Thermal Sensitivity - Method Comparison (Table 1-11), and the New Multi-temperature Precision Study (Table 10-1 & 10-2).

For the other three studies where data was reduced in this manner (Multi-temperature LoB Table 5-1, Multi-temperature LoD Table 5-2, Multi-temperature LoQ Table 5-7, the alternate calibration curves were not specifically generated as part of the original study. The curves do, however, represent valid curves that are entirely acceptable for the data reduction performed. The system requires a calibration for each instrument and reagent pack lot combination on which sample measurements will be made. Each calibration has a stored curve stability of 56 days. In all cases, the alternate curves were valid calibrations performed on the same instrument and reagent pack lots as used in the studies to which they were applied. Furthermore, the alternate calibration curves were well within the stored calibration curve stability claim of the device with respect to the studies for which they were used (alternate calibration curves were generated 7-50 days prior to the sample measurements to which they were applied.)

As noted in our response to question 1b, BEC is able to reduce the same raw sample measurement output from multiple calibration curves. As the indicated calibration curves as well within the limitations of the system, this approach is acceptable and represents device performance consistent with the intended use.

Thank you,
Scott

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Caposino, Paula

From: Machen, Valynda (Valynda) L <vmachen@beckman.com>
Sent: Thursday, December 27, 2012 5:09 PM
To: Caposino, Paula
Cc: Cundy, Scott T; Zibman, Chava
Subject: RE: k121214/S001

Dear Paula,

I wanted to let you know that we have received your question and are contacting our development scientists in order to provide you with the answer. Scott will forward this to you as soon as we receive it, as I will be out of the office beginning tomorrow until January 9th.

Best regards,

Valynda

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, December 27, 2012 2:34 PM
To: Machen, Valynda (Valynda) L
Cc: Cundy, Scott T; Zibman, Chava
Subject: RE: k121214/S001

Dear Valynda,
Thank you so much for the response. I do have an additional question. When you recalculated the data, it seems that it was not recalculated against the original calibration curves generated at the same time as the samples were measured. Is this correct?
Thanks,
Paula

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Caposino, Paula

From: Caposino, Paula
Sent: Friday, December 28, 2012 1:00 PM
To: Zibman, Chava
Cc: Biswas, Bipasa
Subject: FW: K121214/S001

Dear Chava,
Please see the response from Beckman Coulter regarding the calibration strategy. I think that the studies described in the first paragraph are valid and can be reviewed. The LoQ, LoB and LoD studies are not valid so let's not look at the recalculated data.
Call me if you have any questions.
Thanks,
Paula
-----Original Message-----
From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Friday, December 28, 2012 12:52 PM
To: Caposino, Paula
Cc: Machen, Valynda (Valynda) L
Subject: K121214/S001

Hello Paula,

In total, results were recalculated against alternative calibration curves for six different studies to respond to the 510k deficiencies outlined by the agency. For three such studies the alternate calibration curves were in deed part of the original study design and were generated at the same time as the samples were measured. The studies include Thermal Sensitivity - Robustness (Table 1-10), Thermal Sensitivity - Method Comparison (Table 1-11), and the New Multi-temperature Precision Study (Table 10-1 & 10-2).

For the other three studies where data was reduced in this manner (Multi-temperature LoB Table 5-1, Multi-temperature LoD Table 5-2, Multi-temperature LoQ Table 5-7, the alternate calibration curves were not specifically generated as part of the original study. The curves do, however, represent valid curves that are entirely acceptable for the data reduction performed. The system requires a calibration for each instrument and reagent pack lot combination on which sample measurements will be made. Each calibration has a stored curve stability of 56 days. In all cases, the alternate curves were valid calibrations performed on the same instrument and reagent pack lots as used in the studies to which they were applied. Furthermore, the alternate calibration curves were well within the stored calibration curve stability claim of the device with respect to the studies for which they were used (alternate calibration curves were generated 7-50 days prior to the sample measurements to which they were applied.)

As noted in our response to question 1b, BEC is able to reduce the same raw sample measurement output from multiple calibration curves. As the indicated calibration curves as well within the limitations of the system, this approach is acceptable and represents device performance consistent with the intended use.

Thank you,
Scott
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Caposino, Paula

From: Caposino, Paula
Sent: Thursday, December 27, 2012 9:39 PM
To: Zibman, Chava
Cc: Biswas, Bipasa
Subject: Update on Troponin--my prioritization

Dear Chava,
I am still waiting on Beckman Coulter to confirm the recalculation strategy, although, I am pretty sure they will confirm that it was done with a new calibration curve. With that in mind, I wanted to update my request.

I think we have to look at the data from the response and the data from the original submission that I sent you today for several studies. Let me know if there is any raw data from the original submission that you would like to have so I can send Beckman that request.

Regarding deficiency 1a, please consider the original method comparison data, the pre verification concordance study and the repeated thermal sensitivity study. For all of these, can you please perform regression analysis comparing all temperatures (using singlicate data for the test). Can you verify that the performance at values less than 0.1ng/mL and can you look at the concordance against the 0.03 ng/mL cut-off (for all samples and then for samples less than 0.1ng/mL.

For the LoQ, I am at a loss. They have pooled all data according to ambient temperature. I do not believe this data is poolable since the study design was very different for each of the 3 different studies. Furthermore, they have also included recalculated data in the pooled estimates. I don't think we can use the recalculated data which leaves us with the data from the original submission that I emailed you today. I think we should look at the 3 different studies separately and see what the LoQ is at 10%CV and 20%CV for the different studies. I still think they need to define it based on the worst case—which is how I understand EP17.

I think they need to repeat linearity so don't worry about it.

I will need a stat consult on the field effectiveness study to see what that data is demonstrating. This will be in the original submission that I sent to you. I did not see a bias analysis which I thought was necessary to demonstrate that the device is reliable across temperatures at actual labs. This was addressed in deficiency 7.

Precision looks ok (this is deficiency #10). Let me know what you think. The original data is in the file that I emailed you. Regarding the stability studies, I do not understand the Z term that they use. Is this appropriate? The graphs for reagent stability definitely show issues (replicates way outside the acceptable area). I will have questions about this but want to see what you think of their analysis.
You probably think I am going crazy and I am. This is the worst time for me to get a problem submission back on my clock. I will put this submission back on hold (not make a decision) since the response, I believe, is still underwhelming.

Thank you Chava.

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Caposino, Paula
Sent: Thursday, December 27, 2012 4:01 PM
To: Zibman, Chava
Subject: concordance studies

If seems that the new concordance studies may have more samples above the cut-off (70% compared to 50% in the original experiment). We should get an idea of how many samples in the concordance studies are between 0-0.06ish ng/mL (which are the critical values)
Thanks
P

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
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Caposino, Paula

From: Caposino, Paula
Sent: Thursday, December 27, 2012 3:58 PM
To: Zibman, Chava
Subject: Loq data from original submission
Attachments: AccuTnI 510(k) Access2 reduced.pdf

Please look at 8.3 for the LoQ data (this is the entire 510(k)). Based on this data, we should figure out what the LoQ is. They are pooling data now but I think we'll have to work off of this data and come to an agreement as to what these experiments support and why.
Thanks,
Paula

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Caposino, Paula

From: Caposino, Paula
Sent: Wednesday, December 26, 2012 12:12 PM
To: Zibman, Chava
Subject: RE: k121214 S001 Troponin assay from Beckman

Chava,
I wanted to also ask that for any method comparisons that we look at singlicate measurements. Beckman has analyzed the data using replicates.
Thanks,
Paula

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Caposino, Paula

From: Zibman, Chava
Sent: Wednesday, December 26, 2012 8:51 AM
To: Caposino, Paula; Biswas, Bipasa
Subject: RE: k121214 S001 Troponin assay from Beckman

Paula, I will do my best to get this done. Thanks for all the information and for being so specific in your questions. I'll be in touch if I need any clarifications.

Chava

From: Caposino, Paula
Sent: Monday, December 24, 2012 4:36 PM
To: Biswas, Bipasa
Cc: Zibman, Chava
Subject: FW: k121214 S001 Troponin assay from Beckman
Importance: High

Dear Bipasa,
I sent this email to Chava today. It is a ton of work and we need to get this done by the first week in January. Not sure if Chava will need help. Should have cc'd you on this from the get go but wanted to keep you in the loop.
Thanks,
Paula

From: Caposino, Paula
Sent: Monday, December 24, 2012 2:26 PM
To: Zibman, Chava
Subject: k121214 S001 Troponin assay from Beckman
Importance: High

Dear Chava,
I am sorry that I did not get a chance to talk to you about the response to the troponin assay. I am on leave but will be checking emails (from you) and taking phone calls (from you) during my vacation. Please review the following for me:

I hope you remember this submission. This is where we found that the troponin value increased depending on the temperature that the assay was run at. Please review the following from Beckman's response. If you need anything, please please please do not hesitate to ask. I do not have much time to make a decision or place the company back on hold.

1. Response to item 1a—Please analyze this new concordance data for bias, imprecision and concordance at all temperatures tested (Beckman seems to have only compared the temperature extremes). The question is, is the bias, imprecision and concordance (in respect to the 0.03 ng/ml cut-off) equivalent irrespective of the ambient temperature at the time of testing. They have provided data from a total of new 10 studies I believe. Can we check them individually and pooled?
2. 1b and 1c Can you analyze the reanalyzed data (Beckman has reanalyzed the data by calculating the result obtained at all different temperatures against a calibration at a single temperature. If you remember, initially they had calibrated and measured the samples at the same temperatures which we said was not as this device is labeled for use). Can we look at this data for bias, imprecision and concordance? Again, the question is, is the bias, imprecision and concordance (in respect to the 0.03 ng/ml cut-off) equivalent irrespective of the ambient

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temperature at the time of testing? Can you please comment on the acceptance criteria (based on an "accepted clinical cut-off of 0.06)????

3. Can you review question 3. These were mostly your questions.
4. Please review question 5 (detection limits). I want to make sure that we agree with their analysis of LoQ. I want to make sure that we are reviewing the data reanalyzed data from the "standardized LoQ study" (Beckman has reanalyzed the data from the standardized LoQ study, by calculating the result obtained at all different temperatures against a calibration at a single temperature. If you remember, initially they had calibrated and measured the samples at the same temperatures which we said was not as this device is labeled for use) to make sure that the data is consistent irrespective of temperature and calibration strategy. We should make sure this is consistent with the data from the multi-temperature study where they calibrated at one temperature and ran the samples at different temperatures. I think they have pooled all of the data in the new study. I want to make sure that the we look at the studies separately to make sure they are giving the same LoQ estimate. We need to evaluate this data per CLSI EP17. My question to you is. What is their LoQ? Is consistent irrespective of temperature?
5. Please review the new linearity analysis. Please figure out the linear range where the device meets a non-linearity of no more than 10% (we do not agree to 16% as they currently propose). Again, please advise if the linearity is the same irrespective of temperature.
6. Please review the response to question 7 "Field effectiveness studies". Is the precision the same irrespective of temperature in these field effectiveness studies?
7. Please review Question 10, is the precision the same irrespective of temperature in the in-house precision studies.
8. Please review question 18. I don't understand their statistical method. Do you agree with their conclusions?
9. The acceptance criteria for the thermal bias is 1% per degree. Do you have any idea how this would affect the clinical performance of this device based on their clinical data? If we assume worst case then we should look at all test results +10% and all test results -10% and see the clinical performance of the device. How does this add to the total error of the device. Is this acceptable. Can you calculate this for me? I am forwarding you the clinical data again in case it got buried in your records.

Chava, I know this is a big job and I really need your help. As we have discussed in the past, this is a big deal. Incorrect troponin values will either release people from the ER in the early phases of a heart attack or send people to the cath lab unnecessarily. Both are problematic especially releasing people inappropriately.

I am completely available to you. Please call me or text me at 240-423-5740 if you need anything. I will be checking my emails in the mornings but if you need something in the afternoon, text me or call me and I will check my emails or we can talk. Do not hesitate.

I am going to forward you the emails that I have sent to Beckman requesting raw data for your review. If you need anything different or additional, let me know and I will ask the sponsor for it.
Thanks Chava.
Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
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Silver Spring, MD 20993
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Caposino, Paula

From: Machen, Valynda (Valynda) L <vmachen@beckman.com>
Sent: Wednesday, December 26, 2012 4:51 PM
To: Caposino, Paula
Cc: Cundy, Scott T; Zibman, Chava
Subject: RE: k121214/S001
Attachments: k121224 Line Data 12262012.xlsx

Hello Paula,

Attached is the data file you have requested.

In response to Question 1, all studies used independent patient samples.

In response to Question 2, none of the samples used in these studies were the same patient samples used in the original concordance study.

I have summarized the location by tab number for each of the raw data sets below.

Study Description	Workbook Tab Number
Confirmatory studies	Tabs 4-10
Repeat concordance study	Tab 3
Pre-verification concordance study	Tab 2
48 samples from the original method comparison study	Tab 1
Deficiency 1b and 1c	Tabs 11, 12
Internal field effectiveness study	Tab 16
External field effectiveness study	Tab 17
LoQ	Tabs 13-15

We are available to assist in anyway with the agency review of the data. Please let us know if a teleconference or face to face meeting would be helpful.

Best regards,

Valynda

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Monday, December 24, 2012 1:50 PM
To: Caposino, Paula
Cc: Machen, Valynda (Valynda) L
Subject: Re: k121214/S001

No problem. Thank you for the clarification though.

Sincerely,
Scott

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, December 24, 2012 01:48 PM
To: Cundy, Scott T
Cc: Machen, Valynda (Valynda) L
Subject: RE: k121214/S001

Hi Scott,
That's great. I am not sure I was very clear on the LoQ studies. I really want to make sure that I also have the raw data for the recalculated LoQ studies with the calibrations at each temperature and the runs at all the other temperatures. These should be clearly labeled so my Statistician can understand the data.
Thanks Scott.
Paula

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Monday, December 24, 2012 1:41 PM
To: Caposino, Paula
Cc: Machen, Valynda (Valynda) L
Subject: Re: k121214/S001

Hello Paula,

We will get you the requested information.

Happy Holidays.

Thank you,
Scott

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, December 24, 2012 01:33 PM
To: Cundy, Scott T
Cc: Machen, Valynda (Valynda) L
Subject: RE: k121214/S001

Dear Scott,
Thanks for your quick reply. I need to make sure that my Statistician has all of the raw data she will need to review the response. Please provide the following as soon as possible as excel files (for the data):

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostics and Radiological Health
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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1. All raw data in response to deficiency 1a (i.e., the confirmatory studies, the repeat concordance study, the pre-verification concordance study, the 48 samples from the original method comparison studies). Please clearly label the data so that FDA can independently analyze it. Please also confirm that all studies used independent patient samples. If studies did not use independent samples, please provide a list of the studies that used the same study samples.

2. Please provide the raw reanalyzed data in response to deficiency 1b and 1c. Please clearly label the data so that FDA can independently analyze it. Please state if any of the samples used in these studies were the same patient samples used in the original concordance study (which you describe as anomalous).

3. Please provide the raw data for the field effectiveness studies. Please clearly label the data so that FDA can independently analyze it.

Thank you very much. Please let me know when you will have this data. It should really not be later than COB on the 26th.
Regards and happy holidays.
Paula
Again, please cc chava.zibman@fda.hhs.gov on all communications.

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Monday, December 24, 2012 1:05 PM
To: Caposino, Paula
Cc: Machen, Valynda (Valynda) L
Subject: Re: k121214/S001

Hello Paula,

I received your email request. We will provide you with the requested information as quickly as possible.

Thank you,
Scott

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, December 24, 2012 12:03 PM
To: Cundy, Scott T
Cc: Machen, Valynda (Valynda) L
Subject: k121214/S001

Dear Scott and Valynda.
Do you think I could get the LoQ data in excel files? Please provide the data separately for each study (i.e., the study that was performed calibrating the instruments at each temperature separately from the studies that were performed with one calibration at ambient temperature). Also , please provide the data from each instrument separately for each of these studies. Thank you very much.

Please send the data to me and please cc Dr. Chava Zibman too. Her email address is chava.zibman@fda.hhs.gov

Please confirm as soon as possible that you received this request.

Thank you very much and Happy Holidays.
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cundy, Scott T [STCundy@beckman.com]
Sent: Monday, November 19, 2012 7:33 PM
To: Caposino, Paula
Cc: Machen, Valynda (Valynda) L
Subject: RE: Follow up to our teleconference regarding k121214
Attachments: BEC-FDA 10-26-12 F2F Mtg Tnl Thermal Slides.pdf

Hello Paula,

Here is the information that you requested.

November 16, 2012 Participants:
Scott Cundy – VP RA/QA
Stephen Gaston – Director R&D
Jeff Budd – Biostatistician
Corey Carlson – Staff R&D
Cheryl Hodges-Savola – Clinical Research

October 26, 2012 Participants:
Clair O'Donovan; PhD – Sr. VP RA/QA
Scott Cundy – VP RA/QA
Valynda Machen – RA Manager
Stephen Gaston; PhD – Director R&D
Jeff Budd; PhD – Biostatistician
Corey Carlson; PhD – Staff R&D
Marian Navratil; PhD – Manager R&D
Jeff Gibbs - Hyman, Phelps & McNamara – Representing BEC

Thank you,
Scott

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, November 16, 2012 12:35 PM
To: Cundy, Scott T
Subject: Follow up to our teleconference regarding k121214

Dear Scott,
Thank you very much for taking the time to update the agency on your progress. As I said in my last email, I am finalizing the meeting minutes from the October 26, 2012 meeting. Unfortunately, I can't seem to read everyone's name from the participant log. Can you provide me with a list of the participants including their titles (I would also appreciate a list of the participants from today's teleconference as well)?

On a separate note, I wanted to let you know that it seems that the agency has not yet recognized the updated EP17-A2 guideline. I recommend that in your reply, you refer to the recommendations in the EP17-A (which is recognized) guideline.

Thanks and I look forward to hearing back from you.

Regard,
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4) Deficiency Meeting and Discussion

(b)(4) Deficiency Meeting and Discussion

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Caposino, Paula

From: Cundy, Scott T [STCundy@beckman.com]
Sent: Thursday, November 15, 2012 4:11 PM
To: Caposino, Paula; Machen, Valynda (Valynda) L
Subject: RE: Proposed teleconference-briefing document attached

Hello Paula,

Thank you for the note. In preparation for tomorrow's meeting, I'm hoping you can clarify a point that you made below. I believe you are saying that the agency cannot provide feedback on the information that we provided in yesterday's pre-read materials. However, if we have "new" questions, we can discuss those tomorrow. Is that correct? BEC was only planning to discuss the materials provided in our pre-read materials.

Does the agency have any clarification questions on the information that we provided yesterday. If the agency cannot comment on yesterday's pre-read materials and do not have clarifying questions to ask, then I'm wondering if we should cancel the meeting. Thoughts?

Please feel free to call me to discuss.

Thank you,
Scott
(612) 804-1728 Cell

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, November 15, 2012 2:04 PM
To: Machen, Valynda (Valynda) L
Cc: Cundy, Scott T
Subject: RE: Proposed teleconference-briefing document attached

Dear Valynda,
Thank you for the document you provided in advance of our teleconference tomorrow. I have carefully read through it. It appears that you have provided proposed responses to several deficiencies. Please note that we will not be able to discuss whether these responses are acceptable during the teleconference. The reason is that we need to review your complete response to make our decision. We provided recommendations for how you can resolve the deficiencies in our letter requesting additional information. We also provided clarification and additional recommendations in the feedback emailed to you on November 7, 2012. We are happy to discuss any new issues and to hear about your progress in confirming the root cause of the thermal sensitivity issue with your device.

Let me know if you have any questions.

The following is a list of the FDA participants: Carol Benson, Ruth Chesler, Ian Pilcher, Ileana Elder and myself.

The dial in number is 1-866-610-1742 and the Participant Pass Code is 7295033

Regards,

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Paula

From: Machen, Valynda (Valynda) L [mailto:vmachen@beckman.com]
Sent: Tuesday, November 13, 2012 3:31 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Proposed teleconference-briefing document attached

Dear Paula,

Attached is our briefing document for the 11/16 teleconference.

Best regards,

Valynda

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, November 08, 2012 5:56 PM
To: Machen, Valynda (Valynda) L; Cundy, Scott T
Subject: RE: Proposed teleconference

Dear Valynda,
Can I please get the questions by mid day Tuesday? I need time to review the information you provide.
Thanks,
I will provide a call-in number.
Paula

From: Machen, Valynda (Va lynda) L [mailto:vmachen@beckman.com]
Sent: Thursday, November 08, 2012 5:47 PM
To: Caposino, Paula; Cundy, Scott T
Subject: RE: Proposed teleconference

Dear Paula,

We would like to hold the teleconference from 12-1 eastern on Friday November 16th. We will provide you with our questions mid-day on November 14th. Would you like us to provide the call in number for this meeting?

Best regards,

Valynda

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, November 08, 2012 11:08 AM
To: Machen, Valynda (Valynda) L; Cundy, Scott T
Subject: Proposed teleconference

Dear Valynda and Scott,

We have the following times available for a teleconference on Friday November 16th
12:00 to 1:00PM (for 1 hour)
or

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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2:00 to 2:30PM (1/2 hour only)

Let me know what works best for you.
Thanks,
Paula

Paula Velasco Caposino, Ph.D.
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Silver Spring, MD 20993
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November 13, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
ATTN: Paula Velasco Caposino, Ph.D

SUBJECT: Topics for November 16, 2012 Teleconference
Access AccuTnI on the Access 2 Immunoassay Systems, 510(k) K121214

Dear Dr. Caposino,

Thank you for providing your written feedback regarding the subjects that we were not able to discuss during the October 26, 2012 meeting in Washington DC, and for agreeing to meet with us via teleconference to further discuss these topics.

Beckman Coulter would like to seek alignment with the Division in the following areas, which are described in more detail on the following pages:

- Sample Matrix Comparison
- Natural, Unmodified Patient Sample Rationale
- Calibration Strategy

We have addressed FDA's concerns and have provided additional background information below in preparation for our teleconference with the Division on Friday, Nov. 16.

Sincerely,

Scott Cundy, RAC
VP Quality and Regulatory Affairs

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Sample Matrix Comparison

FDA response: *I cannot find the record of our interaction with you from January 2011 (it does not seem to be part of the Pre-IDE I100255). However, since the cut-offs for troponin assays based on the 99th percentile are much lower than the cut-offs of previously cleared assays, the approach used by the predicate device to obtain clearance for several sample types may no longer be appropriate. Specifically, for the predicate device, the diagnostic cut-off was based on the definition of MI as described by the World Health Organization (0.9 ng/mL). This cut-off is 30 times higher than your ROC determined cut-off and 45 times higher than your cut-off using the 99th percentile. Therefore, we are not sure if the regression model will reliably predict the clinical performance of another sample type using your new and much lower diagnostic cut-offs...*

BEC has located and attached the email correspondence (below) between Dr. Kurtis Bray (BEC) and Dr. Ileana Elder (FDA) for your reference.

BEC has also performed additional statistical analyses of the data from the clinical sample matrix comparison study to demonstrate that the assay will reliably predict the clinical performance of both sample types at the established diagnostic cutoffs.

Please review the material provided below. The additional analyses demonstrate the equivalence of serum and plasma matrices, and we will be prepared to discuss any additional questions you have regarding this topic.

In correspondence with FDA, Beckman asked for specific clarification about requirements for validation of additional matrix types. In an e-mail to lead reviewer, Ileana Elder, dated January 13, 2011 we asked:

> From: krbray@beckman.com [mailto:krbray@beckman.com]
> Sent: Thursday, January 13, 2011 10:28 AM
> To: Elder, Ileana
> Subject: I100255
>
> Dear Dr. Elder,
>
> I am writing with a brief question concerning one point of our specimen testing plans for our ongoing prospective AccuTnI clinical trial for the Access and DxI assay systems.
>
> Our current primary specimen type for TnI measurement is lithium heparin, but we also wish to validate the use of serum and include that in our labeling as well. Thus, consistent with the direction provided in FDA's "Points to Consider" document, and using CLSI guidance EP 09 as a guide, our plan is to test the lithium heparin specimens from entire clinical cohort. The use of serum will at the same time be validated per EP 09 by testing and comparing a sufficient subset of serum specimens from the relevant target clinical population enrolled in our clinical trial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please confirm that this approach is aligned with FDA's expectations for validation of multiple specimen types. Thank you.

Kurt Bray

Kurtis R. Bray, Ph.D.
Director of Clinical Research
Beckman Coulter, Inc.
2470 Faraday Avenue
Carlsbad, CA 92010

Dr. Elder replied via e-mail on January 18, 2011:

"Elder, Ileana" <Ileana.Elder@fda.hhs.gov>

01/18/2011 06:41 AM

Dear Dr. Bray,

Thank you for your question regarding validation of different matrix types for your troponin assay. As indicated in the Points to Consider document from April 2010, we recommend that if you are pursuing more than a single matrix type claim for your device then you should collect and test specimens for each claimed sample matrix, such as whole blood and plasma, to obtain clearance for multiple matrices. If you decide not to include all claimed matrix types in your clinical performance evaluation, then you will need to demonstrate that there is little to no bias between sample types in a matrix comparison study using substantially narrow acceptance criteria. In addition, you will need to include an adequate number of samples around the assay cutoff. The results from your matrix comparison study will be evaluated during the review of your device premarket notification.

Do not hesitate to contact us if you have further questions.

Sincerely,

Ileana

Ileana Elder, Ph.D., RAC, CQA (ASQ)
FDA/CDRH/OIVD/DCTD
Phone: (301) 796-6143

As provided for in Dr. Elder's reply, we did not include all claimed matrix types in our clinical performance evaluation, but instead we demonstrated that there is little to no bias between serum and lithium heparin plasma used in the matrix comparison study. We tested matched serum and lithium heparin plasma specimens from 123 subjects whose TnI levels spanned the assay range.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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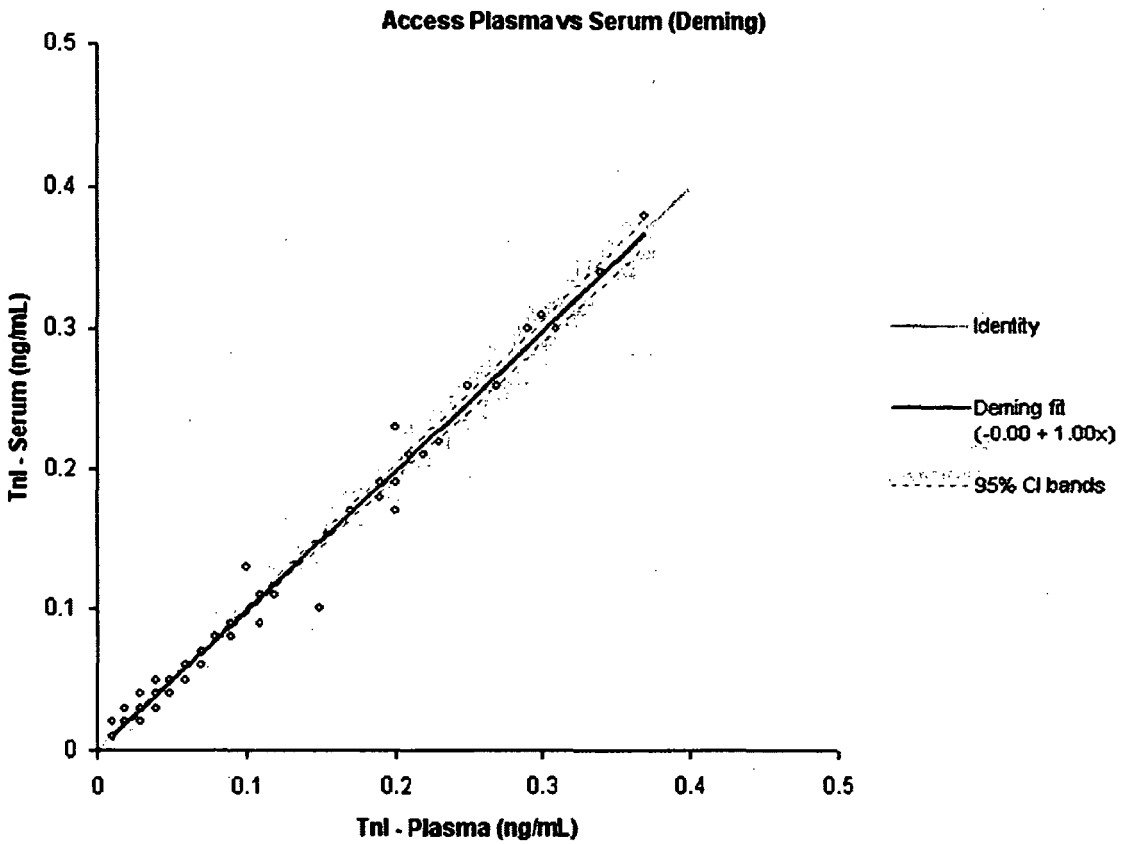
Analytical agreement between the two specimen types was originally tested by Passing-Bablok regression analysis for the 107 subjects whose TnI levels were above 0.01 ng/ml. The excellent agreement shown between the matrices for specimens from the pivotal study as documented in the 510(k) submission (n= 107, slope= 1.00, 95% CI= 0.98 – 1.00, Y intercept= 0.00, r= 1.00) demonstrated the equivalence of serum to plasma as sample matrices for the AccuTnI assay.

To address Dr. Elder's instruction that we focus on patients near the clinical cut off, we have performed a Deming regression analysis on those paired serum and plasma samples within the pivotal clinical trial with troponin levels from 0.01 to 0.4 ng/ml. Similar to what was observed in the wider range analysis, excellent agreement between the two matrices was observed. n= 86, slope= 1.00, Y intercept= 0.00, r= 0.99. See figure below:



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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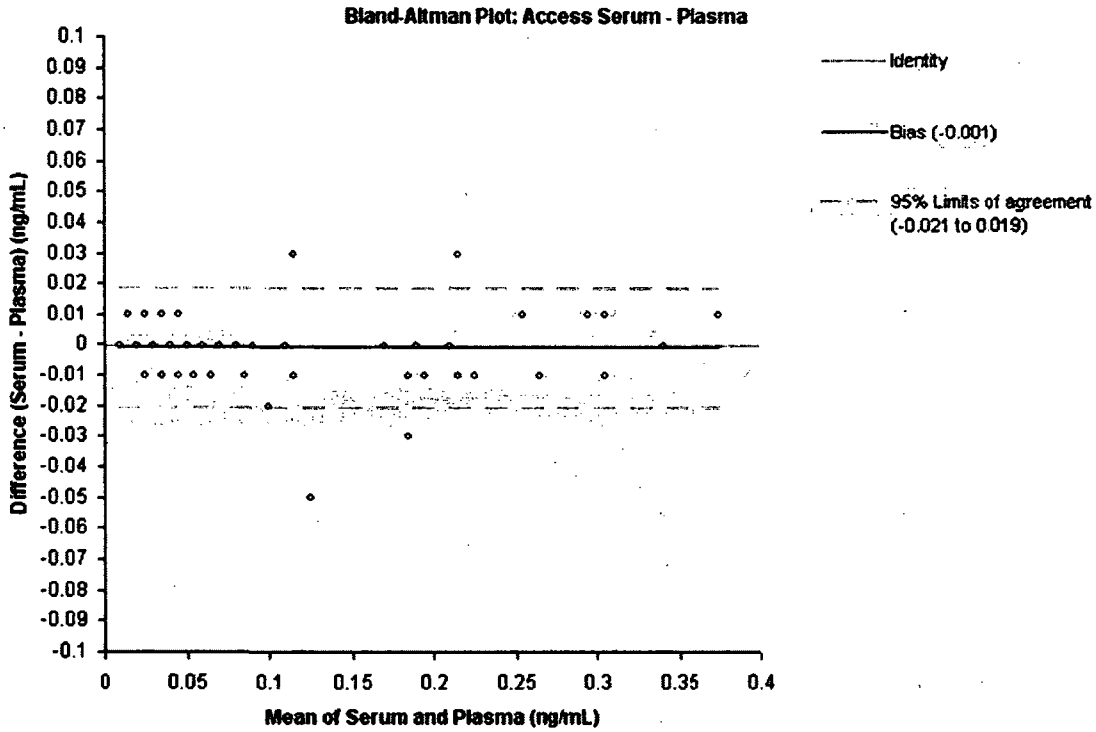
To further assess the agreement between the two matrix types, we also performed a Bland-Altman analysis of bias for the same specimens with values in the clinically-relevant range between 0.01 and 0.40 ng/ml. As the Bland-Altman plot below shows, there was only a small degree of random distribution around a near-zero bias (-0.001), indicating no systemic bias between the two sample matrix types.



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Next, to investigate the clinical concordance between the two sample types around the 0.03 ng/ml recommended clinical cut-off, we performed McNemar's test on the serum and plasma data from all 123 subjects for which both specimen types had been tested. The table below shows excellent concordance with no significant differences (p=0.65) between serum and lithium heparin plasma.

Access AccuTnI: Plasma vs Serum Concordance Analysis
McNemar's Test: p=0.65
96% agreement between plasma and serum (118/123)

	Serum <0.03	Serum ≥0.03	Total
Plasma <0.03	38 (30.9%)	3 (2.4%)	41 (33.3%)
Plasma ≥0.03	2 (1.6%)	80 (65.0%)	82 (66.7%)
Total	40 (32.5%)	83 (67.5%)	123 (100%)

Finally, to further examine the clinical utility of the matched serum and plasma specimens from the pivotal trial, we constructed Receiver Operating Characteristic curves (ROC) for each matrix using all subjects with both serum and plasma test results. As shown in the figure on the next page, the two specimen types showed equivalent diagnostic efficacy. The areas under the ROC curve (AUC) are **0.845** and **0.847** for plasma and serum, respectively.

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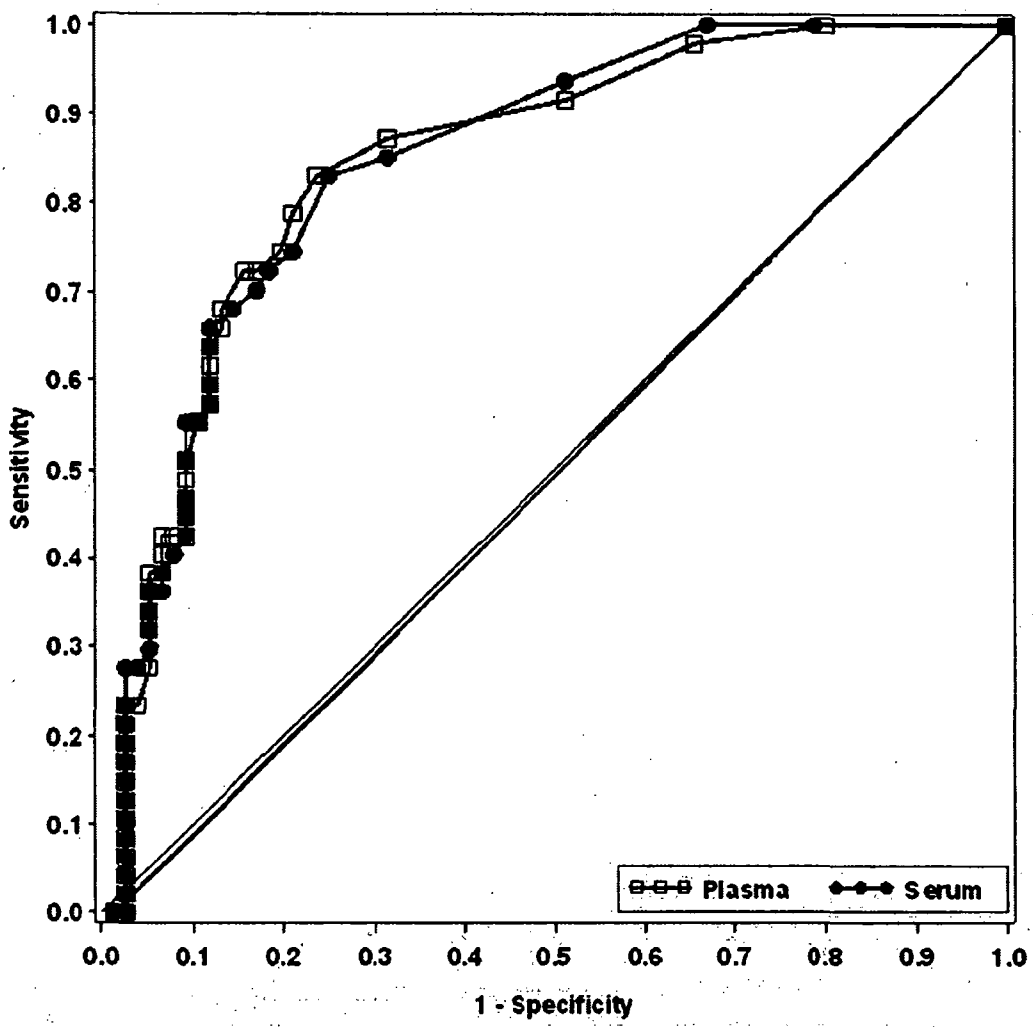
ROC Curves, Plasma vs. Serum
Study Tnl - Access
Adjudicator Diagnosis



N_{MI}	N_{Non-MI}	Matrix	AUC	95% Confidence Interval	p-value
47	76	Plasma	0.845	0.775 - 0.916	0.876
		Serum	0.847	0.778 - 0.915	
p-value for comparison of AUCs between serum vs. plasma samples					

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Following the direction from FDA, BEC has demonstrated a high degree of agreement in correlation, concordance, lack of bias, and equivalent diagnostic efficacy between serum and lithium heparin plasma for specimens both near the clinical cut-off and at higher levels. This high degree of agreement is confirmed by the results of the independent, internal analytical matrix comparison studies described in the 510(k) submission.

Therefore, we maintain that the data clearly justify the use of serum, and that the claim for both sample matrices be retained in our statement of Intended Use. / THIS IS A RESPONSE

Natural, Unmodified Patient Sample Rationales

FDA Response: *We still recommend that you provide data for all requested studies using natural patient samples (i.e. not spiked with exogenous cTnI analyte). However, we agree that the use of pooled patient samples with relevant cTnI concentrations (that are not spiked with exogenous cTnI analyte) are acceptable for the requested studies (i.e., LoD, LoQ, field effectiveness studies and precision studies).*

BEC confirms that natural patient pools with relevant cTnI concentrations (i.e., not spiked with exogenous cTnI analyte) were used for LoD, LoQ, and precision studies.

Please review the Field Effectiveness study information provided below. BEC believes that the use of commercial quality control materials in these studies is appropriate, and that the results demonstrate the effectiveness of the thermal algorithm under a variety of system and field conditions. We will be prepared to discuss any additional questions you have regarding this topic.

The Field Effectiveness studies were requested by the Division, and were specifically designed to provide additional confidence that the final AccuTnI product in its entirety, including thermal algorithm, system software, assay protocol files, etc., performs properly on fielded instruments. The study design challenged the thermal algorithm under conditions of broader variability than is typically encountered in the clinical laboratory environment, including:

- Multiple instruments of varying vintage
- Multiple ambient temperatures, constant and dynamic
- Multiple reagent lots
- Multiple test request scenarios including STAT, panels, reflex, etc.
- Multiple test scenarios under random access conditions including other assays

Because of the large sample volumes needed for these studies, commercial quality control materials known to emulate natural patient sample thermal behavior were used for the Field Effectiveness studies at internal and external sites. We maintain that the use of natural patient samples in the field effectiveness studies is not necessary because accuracy, precision, and sensitivity of the assay were each verified using natural patient samples and/or pools in other studies conducted according to recognized guidelines. Therefore, the use of quality control

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materials known to emulate the patient samples in response to ambient temperature changes is entirely appropriate for this type of study.

We maintain that the Field Effectiveness studies, using commercial control materials and the wide range of variables included in the study design, provide objective evidence of the robustness of the assay and algorithm when used in a variety of system and field conditions.

Calibration Strategy

FDA response: *In addition to understanding "that even though the calibrator signals do not change with ambient temperature, the system can perform valid calibrations at the extremes of the temperature range with appropriate software algorithm adjustment of sample results", we need to understand the performance of the device as it is intended to be used. Regarding the limits of detection studies (i.e., LoB, LoD and LoQ) while we encourage different sources of variables in your studies, these should be within the context of the expected variability that the end user would experience. As such, it seems that calibrating at every temperature is not as this device is to be used. Therefore, in your response, please provide data for the requested studies demonstrating the performance of this device as intended for use. As discussed above in item 2, in your response, you need to demonstrate that the performance of your device is equivalent irrespective of ambient temperature and that your device is safe for patient use. Furthermore, where there are differences in the performance with calibration at each temperature compared to calibration at a single temperature, you should investigate the reason for the difference in the performance and provide your findings for FDA review.*

Please review the calibration information provided below. BEC believes that the calibration strategy used in these studies is appropriate, and the results demonstrate the effectiveness of the thermal algorithm. We will be prepared to discuss any additional questions you have regarding this topic.

As previously described, the thermal profile of calibrator material is distinct from patient samples and controls. Since the algorithm already accounts for the difference in thermal sensitivity between calibrators and samples, it is immaterial whether a sample is run at the same or different temperature from which the device was calibrated. Therefore, the device performance is not misrepresented in situations where the sample measurements are taken at the same temperature as calibration.

The effectiveness of the algorithm at different calibration temperatures is demonstrated by two independent studies, which allow data reduction from calibration curves generated at multiple, discrete temperatures. The complete datasets including reduction of data from multiple calibration temperature scenarios from "Thermal Sensitivity – Robustness" and "Thermal Sensitivity – Impact on Cross-Temperature Method Comparison," will be provided to the Division as part of our final 510(k) submission response.

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Analytical testing to establish assay detection capability (i.e., LoB, LoD) is fundamentally different from routine testing in the clinical laboratory. BEC's detection capability studies were conducted in conformance with the recognized CLSI guideline EP17-A2, "Detection Capability for Clinical Laboratory Measurement Procedures," and are specifically designed to establish these parameters, and *not* to duplicate end-user testing conditions.

EP17-A2 recommends that manufacturers include multiple reagent lots, multiple calibration cycles, and other variables to establish estimates of LoB, LoD or LoQ to "increase the rigor of the resulting detection capability estimates." If we were to run the study "as it is intended to be used" by the clinical laboratory, then we would sacrifice the rigor of the assay's performance estimates.

Nevertheless, Beckman will provide data and results from LoB, LoD, and LoQ studies where the calibration was performed at multiple temperatures, different from those at which measurements were taken, as part of our 510(k) submission response.

Therefore, we maintain that BEC's detection capability studies, with the added data analysis of multi-temperature calibrations, provide objective evidence for the detection performance claims included in the AccuTnI Instructions for Use.

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MEETING PARTICIPANT LOG

DATE: 10/26/2012

TIME: 10-11

PURPOSE OF MEETING: h/2/214 - Access Troponin (Acu Int)

INDUSTRY

NAME	ORGANIZATION
Marian Navratil	Beckman Coulter
COREY CARLSON	BECKMAN COULTER
SCOTT CUNOY	BECKMAN COULTER
Jeff Budd	Beckman Coulter
Jeffrey Cobb	Hyne Philips Minnaugh
CLAIR O'DONOVAN	BECKMAN Coulter
Valynda Machen	Beckman Coulter
STEPHEN GASTON	BECKMAN COULTER

FDA

NAME	OFFICE/DIVISION/BRANCH
Paula Capozino	OIR/DCTD
AMY GHERING	DCTD/OIR/CDRH
Carol Benson	OIR/DCTD
[illegible]	OIR/DCTD
[illegible]	OIR/DCTD
Ileana Elder	OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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RECORD OF MEETING

Product Name: Access AccuTnI on the Access 2 Immunoassay Systems (k121214)
Sponsor: Beckman Coulter, Inc.
Meeting Date/Time: October 26, 2012, 10-11:00 A.M., WO66-5578
Meeting Format: Face-to-Face meeting
Meeting Recorder: Amy Ghering

FDA Attendees:
Paula Caposino, Lead Reviewer, Office Of In Vitro Diagnostics And Radiological Health (OIR), Division Of Chemistry And Toxicology Devices (DCTD)
Amy Ghering, Reviewer, OIR/DCTD
Ian Pilcher, Reviewer, OIR/DCTD
Ileana Elder, Compliance Team Leader, OIR/DCTD
Ruth Chesler, Branch Chief, OIR/DCTD
Carol Benson, Deputy Division Director, OIR/DCTD

Beckman Coulter, Inc. (BEC) Attendees:
Clair O'Donovan; PhD – Sr. VP RA/QA
Scott Cundy – VP RA/QA
Valynda Machen – RA Manager
Stephen Gaston; PhD – Director R&D
Jeff Budd; PhD – Biostatistician
Corey Carlson; PhD – Staff R&D
Marian Navratil; PhD – Manager R&D
Jeff Gibbs - Hyman, Phelps & McNamara – Representing BEC

Subject: To discuss the results of BEC's investigation of the root cause of the persistent thermal sensitivity observed in the Thermal Sensitivity – Impact on Low Dose Concordance/Agreement study ("concordance") despite the use of the corrective algorithm.

Items Discussed: Root cause investigation of persisting thermal sensitivity issue: BEC presented data from 4 concordance studies and an analysis of the low concentration samples of the method comparison study (from the 510(k)). One of the concordance studies was performed in the development phase (study 1), one was the concordance study included in the 510(k) (study 2) and two were new concordance studies with newly acquired samples (studies 3 and 4). BEC stated that the only study that showed persisting thermal sensitivity, by using the Passing-Bablok regression method, was the study submitted in the 510(k) to FDA (study 2). BEC stated that the majority of the samples used in this study were obtained from one vendor. BEC explained that this vendor stores samples under conditions that are not appropriate for their device (i.e., stored refrigerated for 2 to 6 weeks while the assay is intended for use on samples stored refrigerated for no more than 24 hours). Therefore, BEC concluded that the root cause for the persisting thermal sensitivity observed in concordance study 2 was improper sample handling.

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BEC stated that when samples are handled according to the instructions in the package insert of the device, they do not observe thermal sensitivity.

FDA expressed concern because samples from that same vendor have been used in at least concordance study 1 and did not demonstrate thermal sensitivity. Furthermore, BEC has subsequently obtained samples from the vendor and has not been able to replicate the thermal sensitivity observed in the data submitted to FDA. FDA recommended that the sponsor specify exactly how many of the samples that demonstrated thermal sensitivity in concordance study 2 were obtained from the vendor in question. FDA reiterated that the limit of quantitation studies and the linearity studies also demonstrated temperature sensitivity. Therefore, FDA is still concerned that the software algorithm may not have corrected the temperature sensitivity issue of this device.

FDA stated that BEC needs evidence to support that sample handling and storage was the problem in the data set provided to FDA. It will be difficult for the agency to determine that this device is substantially equivalent without evidence that the software algorithm is adequate and properly validated instead. Regarding any supportive evidence from modeling experiments using recombinant troponin, the agency expressed concern that the results from the modeling experiments may not reflect the performance of patient samples. The agency also expressed concern that BEC has not performed a study replicating the handling and storage conditions of the patient samples obtained from the vendor used in concordance study 2 that they believe led to thermal sensitivity. FDA understands that this is a complicated issue. However from a public health perspective, BEC needs to provide evidence that this device is safe. FDA needs to have confidence that the device will give the correct troponin test result. The agency is concerned that BEC has provided a hypothesis for the root cause of the thermal sensitivity issue that persists despite the use of the corrective algorithm and BEC will need to provide convincing data supporting that hypothesis. Finally FDA stated that while in the deficiency letter the bias observed in concordance study 2 was described using Passing-Bablok regression, the agency also reviewed the data (and will review all future data) taking into account the fact that this test is both qualitative and quantitative. The agency will also look at the different temperatures (i.e., not just a comparison between the temperature extremes).

To conclude, FDA agreed to provide written feedback on the additional topics BEC provided in the briefing package submitted in advance of this meeting that were not discussed at the meeting.

Reviewer Name and Signature:

Paula V. Caposino
2012.12.05 09:39:18 -05'00'

Paula Velasco Caposino, Ph.D.
FDA/CDRH/OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4) Deficiency Meeting Presentation

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(b)(4) Deficiency Meeting Presentation

(b)(4) Deficiency Meeting Presentation

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Caposino, Paula

From: Cundy, Scott T [STCundy@beckman.com]
Sent: Wednesday, October 17, 2012 10:39 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: Fw: Beckman Coulter AccuTnI on Access 510(k) K121214 - October 26, 2012 Briefing Materials
Attachments: Beckman Coulter -FDA Briefing Materials for TnI 10-17-12.pdf

Hello Paula,

Attached are the briefing materials that I mentioned that I would send. The briefing materials provide additional information that we wish to discuss with you on October 26, 2012.

Please let me know if you have any questions.

Thank you,
Scott Cundy
(612) 804-1728 cell

From: candeecundy@comcast.net [mailto:candeecundy@comcast.net]
Sent: Wednesday, October 17, 2012 10:25 PM
To: Cundy, Scott T
Subject: Beckman Coulter AccuTnI on Access 510(k) K121214 - October 26, 2012 Briefing Materials

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Caposino, Paula

From: Scott T Cundy [STCundy@beckman.com]
Sent: Thursday, October 04, 2012 10:48 AM
To: Caposino, Paula
Subject: RE: Access AccuTnI on the Access 2 Immunoassay System (k121214)

Thank you so much.

Talk to you then.

Scott

BECKMAN
COULTER
We're better together

Scott T. Cundy, RAC
Vice President Quality & Regulatory Affairs

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318

Tel: (952)368-2014
Fax: (952)368-7610
stcundy@beckman.com
www.beckmancoulter.com

From: "Caposino, Paula" <Paula.Caposino@fda.hhs.gov>
To: Scott T Cundy <STCundy@beckman.com>
Date: 10/04/2012 09:13 AM
Subject: RE: Access AccuTnI on the Access 2 Immunoassay System (k121214)

Dear Scott. Before I forget, please find enclosed the dial in number for our teleconference today from 2-3 EST.

Dial in Number:1-866-506-3210, Participant Pass Code:8496279

FDA participants are:
Courtney Lias, Carol Benson, Ruth Chesler, Ileana Elder, Ian Pilcher and myself.

Talk to you then.

Thanks,
Paula

From: Scott T Cundy [mailto:STCundy@beckman.com]

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Sent: Monday, October 01, 2012 12:28 AM
To: Caposino, Paula
Cc: Valynda Machen
Subject: Re: Access AccuTnI on the Access 2 Immunoassay System (k121214)

Hello Dr. Caposino,

Thank you very much for the email and meeting request. We would like to accept the Thursday 2-3 pm EST option, if that still works for the agency.

If there are specific questions that you would like for us to address, please let me know so that we are sure to have the appropriate person / answer available. Otherwise, we will be prepared to provide a general update on the program.

Thank You,
Scott

(612) 804-1728 cell.

From: "Caposino, Paula" [Paula.Caposino@fda.hhs.gov]
Sent: 09/28/2012 04:44 PM GMT
To: Scott Cundy
Cc: Valynda Machen
Subject: Access AccuTnI on the Access 2 Immunoassay System (k121214)

Dear Mr. Cundy,
Dr. Courtney Lias has asked me to set up a teleconference with your team next week to get an update regarding your response to the deficiencies identified during our review of the Access AccuTnI on the Access 2 Immunoassay System (k121214). We are available next Tuesday October 2nd from 11-12 PM or next Thursday October 4th from 2-3 PM. Please let me know if your team is available on either of these days. Dr. Lias requests that Dr. Clair O'Donovan also participate in the teleconference.

Thank you in advance of your response.

Regards,

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIVD, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 17, 2012

BECKMAN COULTER, INC.
1000 LAKE HAZELTINE DR.
CHASKA, MINNESOTA 55318-1084
ATTN: VALYNDA MACHEN

510k Number: K121214

Product: ACCESS ACCUTNL REAGENT AND

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Pleaseremember that all correspondence concerning your submission MUST be sent to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. On August 12, 2005 CDRH issued the Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s. This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so in 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely,

510(k) Staff

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EXPLANATION FOR ECOPY ATTACHMENT

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Instead, FDA is providing you with this information so that you can understand the reasons why your eCopy failed in order to better assure that an eCopy that you submit for another submission will not have similar issues.

As additional resources:

- Refer to our eCopy guidance at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf. The eCopy program is not implemented (i.e., eCopy remain voluntary) at this time; however, the technical specifications/standards in Attachment 1 of the guidance are already in place.

- We strongly encourage you to take advantage of our free new eSubmitter-eCopies tool at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm317334.htm, which will help create an eCopy that passes the new technical specifications/standards.

Please keep in mind that once we implement the new eCopy program, most submissions types will go on eCopy hold until a valid eCopy is received.

If you have any questions about the eCopy program or the technical specifications/standards, please contact Ms. Samie Allen at samie.allen@fda.hhs.gov or at 301-796-6055.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment

Attachment for Submission Number(s):

K121214/S001

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1. **The cover letter did not include an adequate eCopy statement.**

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2. **The following PDF file(s) have an invalid naming convention (e.g., numbering scheme incorrect, no underscore between number and descriptive name, descriptive name includes prohibited special characteristics):**

   Access AccuTnI+3 k121214 Response Final-121412-Signed.pdf

   Appendix Final 12-13-12.pdf

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Pugh, Dominique *

From: Microsoft Outlook
To: vmachen@beckman.com
Sent: Monday, December 17, 2012 2:34 PM
Subject: Relayed: K121214 AI LETTER & ECOPY ATTACHMENT

Delivery to these recipients or groups is complete, but no delivery notification was sent by the destination server:

vmachen@beckman.com (vmachen@beckman.com)

Subject: K121214 AI LETTER & ECOPY ATTACHMENT

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K-48 K121214 | S001

BECKMAN COULTER

FDA CDRH DMC
DEC 17 2012
Received

December 14, 2012

Paula Velasco Caposino, Ph.D.
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center-W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-002

RE: 510(k) #k121214
Access AccuTnI+3 on the Access 2 Immunoassay Systems

Dear Dr. Caposino:

This communication responds to questions and concerns expressed by FDA in its June 20, 2012 letter ("Letter") regarding Beckman Coulter ("BEC")'s Section 510(k) premarket notification ("Submission") of intent to market the Access AccuTnI on the Access 2 Immunoassay Systems. BEC has carefully considered each point FDA ("FDA" or "the Agency") has raised in the Letter and has organized the body of this response ("Response") according to the 21 numbered sections/questions in the Letter. We have provided a comprehensive response to each numbered question or concern, each prefaced by the excerpt from the Letter. Each of FDA's 21 numbered items in the Letter is designated as a "question" and referenced within this Response as Question 1.a.i., Question 5.d., etc.

In addition, we have provided an Executive Summary. The purpose of the Executive Summary is to:

- ◊ Demonstrate that BEC has resolved the thermal sensitivity issue in the AccuTnI+3 assay, through a thorough discussion of each of the items identified in Question 1, and
- ◊ Demonstrate that the concerns described in FDA's questions about LoQ and linearity are distinct from and unrelated to the concerns identified in Question 1.
  - Note: FDA has stated in communications, that it considers the concordance, LoQ, and linearity issues all to be indicative of an underlying thermal sensitivity issue. However, as we explain in the Executive Summary, each of these three items is separate and distinct, and the study results cited in the Letter concerning these three issues do not have a common, underlying thermal cause.
- ◊ Demonstrate through the results of both the clinical and analytical studies that with the introduction of the thermal algorithm, the AccuTnI device is safe and effective and substantially equivalent.

This Response incorporates the results from multiple new studies at BEC, reanalyzing data and results from previous, comprehensive studies, and interaction with the Agency's team of reviewers.

BEC initially began working with the Agency on the content of this premarket submission in March 2010, via the pre-IDE process (I100255). A face to face meeting was held in May 2010, and the content of the pre-IDE was updated to address FDA's feedback. After FDA issued its Letter to Manufacturers of Troponin Assays in October 2010, BEC contacted the Agency to confirm that the proposed studies in the pre-IDE were in alignment with the October 2010 letter.

After the notification of the thermal recall to customers and to FDA in April 2011, BEC submitted an update to our original pre-IDE (I100255/S002) to incorporate proposed changes to the analytical performance and system software testing to reflect the addition of a thermal algorithm. Following a teleconference with the Agency in July 2011, study designs were updated to address FDA's feedback.

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Since submitting its 510(k) in April 2012, BEC has had multiple interactions with the Agency, including eight FDA requests for line data, study durations, and information about the temperature equilibration of the Access 2 instruments during the weeks immediately following the Submission. In addition, BEC met with Agency reviewers via teleconference or in a face-to-face meeting on three different occasions between October 4 and November 16, 2012. In the most recent (November 16, 2012) teleconference, the Agency indicated that it was unable to provide feedback on specific elements of the proposed BEC response outside of the context of the entire Response. BEC looks forward to engaging in an interactive review process per the recently published "Improvements in Device Review: Results of CDRH's Plan of Action for Premarket Review of Devices," once FDA has had the opportunity to review the entire Response.

As indicated in the heading above, BEC has changed the name of its troponin assay from "AccuTnI" to "AccuTnI+3," since filing our Submission with the Agency last April. In most instances the new product's commercialized name is reflected in this Response. However, we have not changed the device name in any of the controlled documents and records cited in the Submission or in this Response.

If there are questions regarding this submission, you may contact me by telephone at (952) 368-1383, by fax at (952) 368-7610, or by e-mail at vmachen@beckman.com.

Sincerely,

Valynda Machen, CQA, RAC (US)
Senior Manager, Regulatory Affairs

Enclosure

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BECKMAN COULTER

FDA CDRH DMC

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Received

December 14, 2012

Paula Velasco Caposino, Ph.D.
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center-W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-002

RE: 510(k) #k121214
Access AccuTnI+3 on the Access 2 Immunoassay Systems

Dear Dr. Caposino:

This communication responds to questions and concerns expressed by FDA in its June 20, 2012 letter ("Letter") regarding Beckman Coulter ("BEC")'s Section 510(k) premarket notification ("Submission") of intent to market the Access AccuTnI on the Access 2 Immunoassay Systems. BEC has carefully considered each point FDA ("FDA" or "the Agency") has raised in the Letter and has organized the body of this response ("Response") according to the 21 numbered sections/questions in the Letter. We have provided a comprehensive response to each numbered question or concern, each prefaced by the excerpt from the Letter. Each of FDA's 21 numbered items in the Letter is designated as a "question" and referenced within this Response as Question 1.a.i., Question 5.d., etc.

In addition, we have provided an Executive Summary. The purpose of the Executive Summary is to:

- ◊ Demonstrate that BEC has resolved the thermal sensitivity issue in the AccuTnI+3 assay, through a thorough discussion of each of the items identified in Question 1, and
- ◊ Demonstrate that the concerns described in FDA's questions about LoQ and linearity are distinct from and unrelated to the concerns identified in Question 1.
  - Note: FDA has stated in communications, that it considers the concordance, LoQ, and linearity issues all to be indicative of an underlying thermal sensitivity issue. However, as we explain in the Executive Summary, each of these three items is separate and distinct, and the study results cited in the Letter concerning these three issues do not have a common, underlying thermal cause.
- ◊ Demonstrate through the results of both the clinical and analytical studies that with the introduction of the thermal algorithm, the AccuTnI device is safe and effective and substantially equivalent.

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Sincerely,

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Executive Summary: Analysis of Thermal Issue

FDA has stated that BEC has not resolved the AccuTnI+3 thermal sensitivity issue. This concern was expressed in its Letter in conjunction with questions regarding concordance, LoQ, and linearity. Specifically, in Question 1 of the Letter, the Agency said, "Based on the results of the thermal sensitivity-impact on low dose concordance/agreement study, the LoQ studies and the linearity study, we have serious concerns that you have not resolved the temperature sensitivity issue of your assay."

The purpose of this Executive Summary is to:

- ◊ Demonstrate, through a discussion of each of the items identified in Question 1, that BEC has resolved the thermal sensitivity issue in the AccuTnI+3 assay.
- ◊ Demonstrate that the concerns described in FDA's questions about LoQ and linearity are distinct from and unrelated to the concerns identified in Question 1.
  - Note: It appears that FDA considers the concordance, LoQ, and linearity issues all to be indicative of an underlying thermal sensitivity issue. However, as discussed below, each of these three items is separate and distinct, and the issues identified in the Letter do not share a common, underlying thermal cause.
- ◊ Demonstrate through the results of the clinical and analytical studies that the AccuTnI+3 device with the thermal algorithm is safe and effective and substantially equivalent.

Resolution of Thermal Sensitivity

Results and analysis of test data from over 40 clinical and analytical studies provided in the original submission demonstrate that BEC's thermal algorithm solution effectively reduces the AccuTnI+3 assay's "thermal sensitivity" from approximately 3.5% dose shift per °C to less than 1% dose shift per °C. This represents a substantial reduction in thermal sensitivity and the results of the clinical trial verify that, with less than 1% per °C thermal sensitivity, the medical needs for the device have been met.

Thermal Sensitivity Historical Information

The relationship between temperature change and AccuTnI assay results is well established. As noted in the April 18, 2011, "Urgent Field Safety Notice-Product Correction" letter, BEC's extensive internal testing with a large number of samples showed that when the thermal algorithm is not present, AccuTnI results are inversely proportional to temperature. As the Field Safety Notice states, and as BEC studies have repeatedly shown, AccuTnI results will decrease by approximately 3.5% for every 1°C increase in room temperature and increase by approximately 3.5% for every 1°C decrease in room temperature.

The following table from the recall letter illustrates expected results if a representative patient sample were tested at five different room temperatures without the thermal algorithm:

Table: Example of AccuTnI Results Before Application of the Thermal Algorithm

18°C	21°C	24.5°C	28°C	32°C
0.61 ng/mL	0.56 ng/mL	0.50 ng/mL	0.44 ng/mL	0.37 ng/mL

The Agency has identified low dose concordance/agreement as an area of concern in Question 1 regarding the resolution of thermal sensitivity. Low dose concordance/agreement is addressed below.

Thermal Sensitivity: Question 1

BEC has thoroughly examined the Concordance Study identified in Question 1.a. in relationship to the historical performance of the device described above. One of the first observations was that the % dose shift per °C *prior*

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to the application of the thermal algorithm was not the expected 3.5% per °C. In fact, the majority of samples in this study showed considerably less or even no dose shift with temperature before application of the thermal algorithm, and the results moved in the opposite direction as was to be expected (i.e., results increased as temperature increased) after application of the thermal algorithm. This information led BEC to conduct a full investigation to understand why the samples in this study did not demonstrate the expected thermal behavior. The results of the multiple studies conducted within our investigation clearly show that the concordance data are anomalous, both for the amount and direction of thermal bias displayed and for the amount of uncertainty (scatter) in the results. In other words, the reason the concordance study did not yield the expected result is that the majority of the samples themselves did not demonstrate the expected thermal behavior.

Through this investigation, BEC eliminated a large number of factors that did not contribute to the phenomenon observed in Question 1. Patient samples were subjected to extreme conditions, such as heat treatment, freeze-thaw treatment, and insufficient centrifugation, in an effort to replicate the anomalous thermal behavior. Although BEC has eliminated many potential contributing factors, we have not been able to reproduce the original findings. In all cases, the characteristic thermal behavior of approximately 3.5% change per °C remained, which the algorithm adjusted appropriately.

To further demonstrate that the original study was anomalous, we reanalyzed some original data and conducted several new studies. These activities included:

- ◊ Reanalysis of low end samples from the submitted method comparison data
- ◊ Reanalysis of a pre-verification concordance study,
- ◊ Full repeat of the original concordance study with newly obtained vendor samples, and
- ◊ Seven additional confirmatory studies.

Full study results are provided in our response to Question 1.a. and are summarized below.

- ◊ BEC performed a total of ten additional analyses and/or studies using native patient samples obtained from multiple sources and concluded that the original Concordance Study was anomalous. Passing-Bablok regression slopes for the new studies ranged from 0.90 to 1.08, with most slopes falling between 0.97 and 1.02. Actual results are summarized in the table below.

Table: Summary of Additional Studies

Study Description	Comparison	Passing-Bablok Slope
Method Comparison Low Dose Sample Analysis	18°C vs. 28°C	1.02
Pre-Verification Study Analysis	18°C vs. 26°C 20°C vs. 28°C	1.08 1.00
Concordance Study Repeat	18°C vs. 26°C 20°C vs. 28°C	0.96 0.98
Concordance Confirmatory Study #1	18°C vs. 28°C	0.97
Concordance Confirmatory Study #2	18°C vs. 28°C	0.92

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Study Description	Comparison	Passing-Bablok Slope
Concordance Confirmatory Study #3	18°C vs. 28°C	0.97
Concordance Confirmatory Study #4	18°C vs. 28°C	0.99
Concordance Confirmatory Study #5	18°C vs. 28°C	0.90
Concordance Confirmatory Study #6	18°C vs. 28°C	0.99
Concordance Confirmatory Study #7	18°C vs. 28°C	0.99

- ◊ Because many of the samples used in the Concordance Study shared certain non-standard sample handling histories, sample handling and processing conditions became the primary hypothesis for the investigation of the anomalous thermal profiles of the samples.
- ◊ Exposing newly or previously obtained patient samples to extreme sample handling conditions, however, did not produce the aberrant thermal behavior observed in the samples used in the Concordance Study. In other words, we could not "abuse" other patient samples into behaving like those used in the Concordance Study. Rather, even when subjected to extreme conditions, these samples showed thermal bias and the bias was corrected by the algorithm. (See Appendix 1.) BEC has still not definitively determined the root cause of the anomalous behavior. However, BEC's analysis has shown that the results of the study are anomalous, and that the algorithm addresses thermal sensitivity.

Thermal Sensitivity Question 1 Summary

Based upon the above summary and the extensive analysis in the subsequent sections, BEC believes that we have adequately addressed all of the Agency's questions and concerns regarding the "thermal sensitivity-impact on low dose concordance/agreement study." Because the data provided demonstrates that the algorithm is performing properly, no design modifications were required prior to addressing the remaining deficiency questions. As a result, some responses only required reanalysis of existing data or further explanation, and not a full repeat of the study.

LoQ and Linearity

FDA's expressed concerns that temperature may influence LoQ and linearity are addressed in the sections below.

LoQ-Question 5

BEC has reanalyzed the existing LoQ data per EP-17A, as this version of the standard is currently recognized by the Agency and does not use interpolation in order to determine the results. The full results of this study are provided in our response to Question 5 and are summarized below.

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The results analyzed per EP-17A met the pre-established acceptance criteria of less than 0.06 ng/mL. The lowest concentration sample with less than or equal to the expected imprecision determines the LoQ. The AccuTnI+3 10% LoQ will be reported as 0.03 ng/mL and the 20% LoQ will be reported as 0.02 ng/mL.

These results are different from the Agency's results of 10% LoQ of "0.044 ng/mL at 28 °C, 0.030 ng/mL at NLC and 0.026 ng/mL at 18°C" because of how the data are pooled. Consistent with CLSI guideline EP17-A, to derive a robust estimate around 10% and 20% CV, BEC pooled data from all three instruments (n = 21 samples) at a given temperature, whereas the Agency evaluated each dataset on each instrument (n = 7 samples) individually. Analyzing the sample distribution of each individual sample set (n = 7 on each instrument) is not sufficient to establish an accurate estimate of LoQ. However, when data from all three instruments at a given temperature are combined, there are enough data points near the 10% and 20% LoQ values in order to conduct a robust analysis.

FDA expressed "serious concerns" that the LoQ of the AccuTnI+3 device seems to depend on the ambient temperature. When using EP17-A to assess LoQ results, the estimated LoQ is dependent upon the concentration of the samples used in the studies rather than the temperature at which they were conducted. Due to the nature of the study and use of the EP17-A guideline, one cannot conclude that the derived LoQ is dependent on temperature. Specifically, identical sample sets were not used for studies at all tested temperature conditions thus precluding direct comparison of results in all cases. Furthermore, there is no evidence of residual thermal bias in the LoQ studies, thus distinguishing it entirely from the anomalous concordance study.

The pre-established acceptance criteria for LoQ studies were that 10% total imprecision would be achieved at a concentration less than 0.06 ng/mL and 20% total imprecision would be achieved at a concentration less than 0.03 ng/mL. LoQ results achieved this objective for each temperature condition, and the broadest range results (0.029 ng/mL rounded to 0.03 ng/mL at 28 °C for 10% CV and 0.024 ng/mL rounded to 0.02 ng/mL at 28 °C for 20% CV) are used as the claimed LoQ.

Based upon the above summary and the extensive analysis in the subsequent sections, BEC believes that we have adequately addressed the Agency's questions and have shown that LoQ is not dependent upon ambient temperature.

Linearity-Question 6

In Question 6, the Agency stated that, "the linearity varies depending on the temperature." In addition, the Agency expressed concerns regarding the choice of synthetic matrix as the sample material for this study.

As requested by FDA, BEC has repeated the study using only native antigen and native matrix, and obtained acceptable results. Full study details are provided in our response to Question 6 and are summarized below.

Based on the new study, the linear slope comparing observed and expected results does not show the same temperature dependence that was observed in data provided in the original submission. All reagent pack lot and instrument combinations met the acceptance criteria for linearity at the three ambient temperature conditions tested and demonstrates linearity across the measuring range regardless of calibration and testing temperatures. The AccuTnI+3 assay on Access 2 thus demonstrates linearity, independent of the ambient temperature.

The issues identified in the Linearity section of the Letter are not representative of a failure of the thermal algorithm to appropriately correct patient sample results based on the information provided above. Rather, they resulted from the choice of the calibrator as the linearity sample in the original submission study.

Thermal Sensitivity/LoQ/Linearity Summary

The Agency expressed concerns in its Letter that based upon the results provided for the Concordance, LoQ, and Linearity studies that BEC has not resolved the AccuTnI thermal sensitivity issue.

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In the sections above,

- ◊ BEC demonstrated that we have effectively reduced thermal sensitivity in the AccuTnI+3 assay from the existing 3.5% per °C to less than 1% per °C.
- ◊ The Agency's concern with the thermal sensitivity results from the Concordance study was due primarily to a single anomalous data set. BEC has provided extensive analysis to show that these data resulted from unusual thermal behavior by the samples (not from the thermal algorithm), and has provided a new study and multiple confirmatory studies which met all acceptance criteria.
- ◊ LoQ studies were reanalyzed per EP-17A and met our predetermined acceptance criterion.
- ◊ Linearity studies have been repeated using a native antigen and matrix and show linearity across the measuring range, independent of ambient temperature.
- ◊ BEC has shown that the issues identified with each of the studies above were attributable to different assignable causes and not reflective of a persistent thermal sensitivity issue.

Substantial Equivalence/Safety and Efficacy

As BEC discussed at the two teleconferences and one face-to-face meeting between October 4 and November 16, 2012, BEC has conducted a thorough investigation into the anomalous results of the original concordance study. The lack of thermal sensitivity in the majority of samples in that study cannot be replicated. The inability to identify a definitive root cause for the thermal concordance study in Question 1 should not prevent the Agency from determining that the AccuTnI+3 device is safe, effective, and substantially equivalent. As shown in this Response, multiple concordance studies have shown that the algorithm addresses thermal sensitivity. Moreover, there is a significant amount of other data that supports that the device is safe and effective, and addresses thermal sensitivity. This data is listed below with additional supporting information in the following sections.

1. Low prevalence of an actual significant thermal variation in the field
2. Low prevalence of customer complaints related to thermal bias
3. Health Hazard Evaluation results
4. AccuTnI Market Surveillance Program for over 100 weeks without significant findings
5. Practice of medicine in the United States
6. Extensive analytical testing across temperature extremes
7. Pivotal clinical trial with over 200 MIs, where exceptional results were achieved in the presence of expected laboratory thermal variation

Of note, without the thermal algorithm, the AccuTnI+3 device under review shares the same thermal profile as the device currently on the market. Thus, information on the currently fielded AccuTnI product regarding thermal variation is relevant to this discussion.

1. Low Prevalence of an Actual Significant Thermal Variation in the Field

During the evaluation of Access Hybritech p2PSA (P090026), BEC conducted an extensive analysis on the prevalence of laboratory temperature variation. In this study, the temperatures in 4 laboratories were monitored continuously every 40 minutes over 9 months. A total of 24,685 data points were recorded and during this time and there were no temperature fluctuations > 3°C in a 24 hour time period.

This data indicates that the actual occurrence of large temperature variations in the clinical laboratory is uncommon. If the same degree of temperature fluctuation were applied to the AccuTnI+3 assay, <3% variation in dose results would be observed over a 24 hour time period. For example, at a dose of 0.03 ng/mL, the results would be 0.0309 ng/mL if the temperature decreased by 3°C (which rounds to 0.03 ng/mL) or 0.0291 ng/mL if

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the temperature increased by 3°C (which also rounds to 0.03 ng/mL.) Neither of these test results would by themselves result in a change in patient management, especially since guidelines now recommend serial sampling within 3-6 hours (see Practice of Medicine section 5 below).

2. Low Prevalence of Customer Complaints Related to Thermal Bias in the Existing Access AccuTnI Assay

BEC continuously monitors our customer complaints to determine if any of these complaints are related to thermal bias. Analysis of complaint records from 2/27/2003 to 12/5/2012, show a total of 44 complaints that have been due to thermal sensitivity. No injuries have been reported.

In that same time period, over 135 million AccuTnI tests were sold in the US, resulting in a complaint rate of approximately 0.00003% for AccuTnI thermal issues.

3. Health Hazard Evaluation Results

At the time of the thermal recall in April, 2011, BEC prepared a Health Hazard Evaluation (HHE) to document the risks associated with the thermal issue. This HHE was submitted to the Agency along with the Corrections and Removals Report. The conclusions of the HHE are as follows:

"We conclude that a very small number of laboratories are likely to generate incorrect AccuTnI results due to ambient temperature effects over the lifetime of the instrument. Worldwide laboratory standards and regulations (e.g., ISO 15189 and CLIA regulations) require environmental control and monitoring, and laboratories rarely experience wide swings in temperature. Based on a retrospective analysis of complaints received from Feb. 2003 until Jan. 2011, 29 labs experienced AccuTnI QC shifts that may be due to lab temperature, and only three of these labs in eight years are known to have reported erroneous patient results. None of these results were false negative, and the false positive results were only marginally higher than the upper limit of normal. Therefore we conclude that the probability of a lab reporting a false negative result is remote."

This HHE was prepared to assess the AccuTnI assay prior to the application of the thermal algorithm. The actual risk when the algorithm is applied to AccuTnI results and <1% per °C thermal is present would be even lower.

4. AccuTnI Market Surveillance Program

In September 2010, BEC initiated the AccuTnI Market Surveillance Program. The objectives of the market surveillance program are: (1) to monitor, in as close to real time as possible, the current AccuTnI assay (without the thermal algorithm) on the Access System; (2) to determine if there are any observations of adverse medical events, or events that could lead to adverse medical events, associated with the assay; (3) to determine if these events are attributable to the assay design; and (4) to determine if such events are unusual in type or number from what would be otherwise expected from a troponin assay.

Per the terms of this program, BEC proactively contacts 50 different customers per week and provides the Agency with a monthly report on the outcome of the surveillance program if there are no significant events to report. If significant events are observed, immediate escalation to the Agency is required. Our most recent monthly Agency report dated November 30, 2012 ("AccuTnI Assay Market Surveillance Program Month 28 Report") summarized our findings through 112 weeks of conducting the program. Based on our review of our market surveillance data for the past 112 weeks, the reported events are not unusual in type or number from what would otherwise be expected from a troponin assay. For example, based on the survey information from the 200 accounts contacted during BEC's most recent month of surveillance, there were no indications that the assay was performing outside the established labeling claims and there were no unexpected adverse events attributable to the assay. Please note that these 200 accounts contacted during the most recent month of surveillance represent approximately 5,691 TnI patient samples per day.

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In addition, all results of the market surveillance program have been reviewed for the past 112 weeks and there are no instances of any issues related to temperature variability observed in any of the customer contacts.

It is important to note that the market surveillance program actively collects post market customer data on the performance of the current AccuTnI product that does not contain the thermal algorithm correction. As evidenced above, the current AccuTnI assay is performing as intended and is meeting the customers' needs and expectations. BEC has demonstrated in this Response that with the application of the thermal algorithm, we can even further improve the assay performance while maintaining safety and efficacy.

5. Practice of Medicine in the United States

Serial measurements, looking for a rise and/or fall pattern of cardiac biomarkers, are the standard of care for diagnosis of Myocardial Infarction (MI). With the introduction of highly sensitive cardiac troponin assays in recent years, studies have shown detection of cardiac troponin earlier in the course of the event is possible. Along with the ability to detect lower concentrations of troponin, assays now have the ability to see a dynamic pattern in a shorter time interval.

The Universal Definition of Myocardial Infarction published in 2007 states, "Blood samples for the measurement of troponin should be drawn on first assessment and 6-9 hours later."[1] In 2012, the Third Universal Definition of Myocardial Infarction stated, "Blood samples for the measurement of troponin should be drawn on first assessment and repeated 3-6 hours later."[2] Three hour intervals are common and there are publications that support even shorter, down to one hour, time intervals for serial measurements of troponin.[3]

Because the assessment interval has been shortened to 3-6 hours, it becomes even less likely that large temperature swings will occur in the clinical laboratories during this time period, thus minimizing any thermal effects that may occur. Based on the p2PSA study results and AccuTnI trial results, most laboratories will not see temperature swings of greater than 3-4 °C over a 24 hour time period, which minimizes the thermal variation that occurs while testing a patient.

6. Extensive Analytical Testing

BEC has conducted extensive testing across the extremes of the proposed temperature range for the device. The results of these studies were provided in the original Submission.

These "multi-temperature studies" were conducted at up to six different temperatures, spanning the range of 18°C to 28°C, representing laboratory conditions where large temperature fluctuations may occur, which could influence the AccuTnI results. The results of these multi-temperature studies, which represent the "worst case" conditions of extreme temperature changes that are unlikely to occur in the laboratory, indicate thermal variability of < 1% per °C. These results also indicate that the thermal algorithm is appropriately adjusting sample results across the entire operating range and that the device is safe and effective for use regardless of the ambient operating temperature changes.

7. Pivotal Trial Outcomes

BEC has conducted an extensive clinical trial in support of this submission. A total of 1,929 patients presenting with symptoms suspicious for acute myocardial infarction were evaluated in the Pivotal Trial. Significant diagnostic efficacy was demonstrated in the Pivotal Trial at all time intervals after symptom onset. (See Section 9.0 of the submission for clinical trial details.)

Of significant note, the pivotal clinical trial and external field effectiveness study were conducted under normal laboratory conditions; laboratory temperature was not specifically controlled. However, the temperatures in the laboratory were recorded. The laboratory temperature results are summarized in the tables below.

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Table: Summary of Laboratory Temperatures during the external Field Effectiveness Study

Testing Site	Mean Daily Temp Change	Min Daily Temp Change	Max Daily Temp Change	Min Temp (overall)	Max Temp (overall)
1	0.45 °C	0.2 °C	0.8 °C	22.0 °C	23.6 °C
2	1.7 °C	1 °C	3 °C	21 °C	24 °C
3	2.57 °C	1.7 °C	3.5 °C	23.9 °C	27.8 °C
4	1.6 °C	0.8 °C	3.6 °C	19.9 °C	24.5 °C
5				23.5 °C	25.2 °C

Table: Summary of Laboratory Temperatures during the Pivotal Clinical Trial

Testing Site	Mean Daily Temp Change	Min Daily Temp Change	Max Daily Temp Change	Min Temp (overall)	Max Temp (overall)
1	0.5 °C	0.2 °C	0.7 °C	22.1 °C	23.3 °C
2	2 °C	1 °C	3 °C	21°C	24 °C
3	1.0 °C	0.3 °C	2.3 °C	20.5 °C	24.7 °C
4	1.0 °C	0.1 °C	2.4 °C	17.8 °C	24.0 °C
5	0.9 °C	0.3 °C	1.7 °C	23.1 °C	25.1 °C

The Agency communicated during recent meetings that while the clinical trial results looked favorable, they were representative of only one temperature. However, based on the data above, BEC has shown that the pivotal clinical trial and field effectiveness studies experienced a wide range of temperatures (17.8°C to 27.8°C). In addition, the "Max Daily Temp Change" was less than 4 °C per day, which is consistent with the results observed in the Access p2PSA study where less than 3 °C per day of temperature shift was observed.

These laboratory temperature results show that thermal variation did occur routinely during the course of testing. However, the outcome of the pivotal trial indicates significant diagnostic efficacy in the presence of laboratory temperature variation. This supports that the AccuTnI+3 thermal algorithm is functioning as intended and that the AccuTnI+3 device is safe and effective. That is, in a large-scale, multi-center, multi-laboratory study in which the corrective algorithm was used, and normal laboratory temperature variability was encountered, the clinical trial demonstrated excellent clinical performance. This confirms that the thermal sensitivity issue has been addressed.

Overall Conclusion

BEC has provided extensive objective evidence that the sensitivity issue of the AccuTnI+3 assay has been reduced to <1% dose shift per °C, or <10% dose shift across the entire recommended operating range. The information described in this section, and the thermal data provided in the remaining sections of the Response, demonstrate that the thermal algorithm successfully addresses thermal sensitivity. The anomalous concordance study results are due to a large number of samples with an uncharacteristic thermal behavior which have not been replicated in subsequent studies. BEC believes we have differentiated the results of the LoQ, linearity, and concordance studies, which should dismiss the Agency's concern of a systemic thermal sensitivity issue. Further, BEC has retested and/or reanalyzed the three tests in question per the FDA's request, and have demonstrated both expected and acceptable results. Additionally, the excellent clinical efficacy demonstrated during the pivotal trial confirms the safe and effective use of the device.

In conclusion, the AccuTnI+3 assay with the thermal algorithm correction has been demonstrated to be safe, effective, and substantially equivalent and should be granted FDA 510(k) clearance.

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Response

Question 1: Thermal Sensitivity

FDA: You performed 3 studies to assess the effect of ambient temperature on the AccuTnI assay performance. We have the following concerns with your studies:

1.a. *FDA: Thermal Sensitivity – Impact on Low Dose Concordance/Agreement: Two hundred twenty lithium heparin plasma samples near the clinical cutoff were tested using 2 reagent lots on 2 instruments at 18, 20, 22, 24, 26 and 28°C ± 2°C. Each sample was divided into 3 aliquots and tested at either 18, 22, and 26°C or 20, 24 and 28°C. At each temperature, each sample was run in replicates of 2. A McNemar analysis was performed to determine whether the number of mismatched comparisons was due to random scatter or a systematic difference. In addition, bias between low and high temperature was computed using a log-log regression fit. Your acceptance criteria were that the McNemar p-value must be non-significant (≥0.05). If the p-value is significant, concordance must be ≥90%. Bias at the cutoffs must be ≤0.0084. Please address the following:*

1.a.i. *FDA: You concluded that, in all comparisons of measurements taken on the same sample at different temperatures (averaging the duplicates taken for each measurement), there was agreement in 91% of the cases in terms of whether the values fell >0.03 or ≤0.03 ng/mL. According to our review of the data, of 604 comparisons, both values were at or below the cutoff in 274 cases. Both were above the cutoff in 275 cases. In 2 cases, the value was above the cutoff when measured at the lower temperature but at or below the cutoff at the high temperature. In 53 cases, the measurement was at or below the cutoff when measured at the lower temperature but above the cutoff at the high temperature. The proportion of observations above 0.03 ng/mL varied by temperature as follows:*

Temp	18°C	22°C	26°C
% above cutoff	46.4 (51/110)	47.6 (29/82)	55.55 (61/110)
Temp	20°C	24°C	28°C
% above cutoff	42.7 (47/110)	48.1 (53/110)	57.3 (63/110)

In the case of nearly all discrepancies, a sample was negative at the lower temperature and positive at the higher temperature. We performed further analysis using Passing-Bablok regression. The estimates of the intercepts in these regression[s] was always 0, but, for example, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 with a 95% confidence interval of (1.36, 1.54) and for measurements taken in 18 and 26°C the slope was 1.33 with a 95% confidence interval of (1.26, 1.40). Based on this analysis and the analysis provided in the table above, we have serious concerns that higher temperatures consistently yielded higher troponin measurements. Therefore, we do not believe that the data provided demonstrates concordance across temperatures.

BEC Response to Question 1.a.i.

BEC agrees that the concordance slope in the submitted Thermal Sensitivity-Impact on Low Dose Concordance/Agreement study ("Concordance Study") is 1.46 between 20 °C and 28 °C ambient temperatures.

However, as discussed above in the introductory section, the results of the Concordance Study are anomalous and do not represent the performance of this assay. Indeed, the results of our investigation into the Concordance Study have further demonstrated that the thermal algorithm significantly and substantially reduced the susceptibility of AccuTnI+3 on the Access 2 Immunoassay Systems to changes in ambient temperature.

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The reason the Concordance Study sample set did not, as a whole, demonstrate satisfactory Passing-Bablok slopes is that a large subset of the patient samples tested in that study did not behave like "typical patient samples" and were actually "over-adjusted" by the thermal algorithm. Our evaluation and investigation of the Concordance Study determined that *the thermal algorithm performed exactly as intended* on the samples tested. Specifically, it adjusted the raw TnI measurements upward as ambient temperature increased, to compensate for the inverse correlation between ambient temperature and the "dose response" observed in typical patient samples. In other words, the unacceptable slopes calculated from the Concordance Study data resulted not from a faulty thermal algorithm, but from a set of samples that behaved differently from sample sets used in all other studies.

Adjusting the raw TnI results with the algorithm introduced a completely new bias between measurements taken at different ambient temperatures, in which higher temperatures yielded consistently *higher* troponin measurements on a particular subset of test samples. The overall bias observed in the Concordance Study was in the wrong direction and is therefore uncharacteristic of this device.

Our evaluations and investigations, described in greater detail below, indicate that the thermal behavior of a particular subset of samples used in the Concordance Study was anomalous. BEC's investigation into the aberrant and unexpected sample behavior and its effect on the Concordance Study took two distinct paths:

- ◊ One investigation path involved evaluating newly obtained samples in a series of repeated concordance studies to further assess the performance of the thermal algorithm in the AccuTnI+3 assay and to estimate the magnitude of any residual thermal bias or other unexpected bias.
- ◊ The other path was to investigate the source of the issue(s) that might have caused the anomalous behavior of samples from the original Concordance Study, including their collection and handling histories, to see what they had in common that might have caused them to exhibit such an atypical thermal profile. Refer to Appendix 1 for the "Concordance Root Cause Investigation Report" and to Appendix 2 for additional technical information.

The information presented in the sections below describes the outcomes of these investigations in detail. Here are BEC's major findings and conclusions:

- ◊ BEC performed ten additional analyses and studies using natural patient samples with low troponin I concentrations obtained from multiple sources and concluded that the original Concordance Study was anomalous. Passing-Bablok regression slopes for the studies ranged from 0.90 to 1.08, with most slopes falling between 0.97 and 1.02.
- ◊ Because many of the samples used in the Concordance Study shared certain non-standard sample handling histories, sample handling and processing conditions became the primary hypothesis for the anomalous thermal profiles of the samples.
- ◊ Exposing newly or previously obtained patient samples to extreme sample handling conditions, however, did *not* produce the aberrant thermal behavior observed in the samples used in the Concordance Study. In other words, we could not "abuse" other patient samples into behaving like those used in the Concordance Study.
- ◊ Although BEC has not yet identified the root cause of the behavior of the samples used in the Concordance Study, our investigation has demonstrated that native patient samples, when measured in the AccuTnI+3 assay, are appropriately adjusted by the algorithm under a wide range of sample handling conditions.

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Additional Analysis:

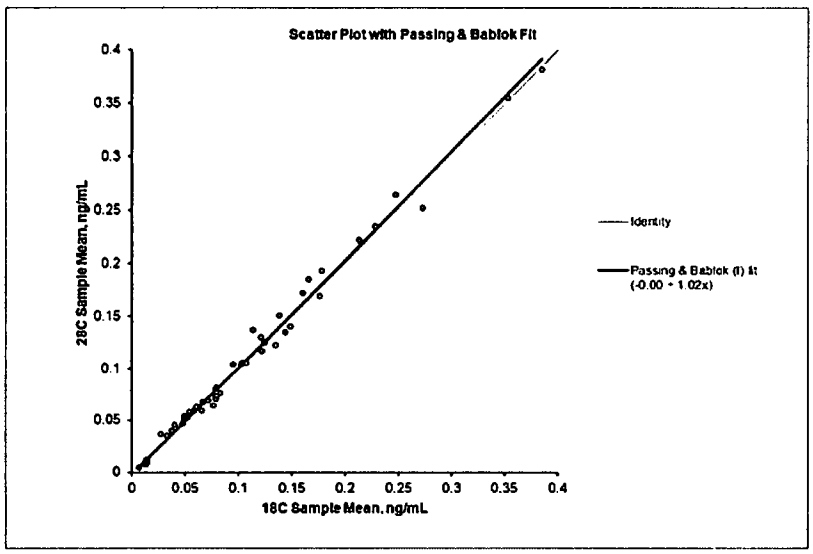
As part of the initial investigation into the cause of the unexpected concordance results, BEC evaluated data from two existing studies containing low-dose native patient samples, looking for a similar aberrant concordance slope.

Reanalysis 1: The originally submitted Thermal Sensitivity-Impact on Method Comparison study (section 8.14) contained 48 samples in the low-dose range of 0.0 to 0.4 ng/mL. These samples had been tested at 18 °C, NLC, and 28 °C. BEC reanalyzed the results from the population of samples in the concentration range of 0.0 to approximately 0.4 ng/mL, and performed a Passing-Bablok regression and Pearson correlation comparing results at 18 °C and 28 °C. The results are shown below in Table 1-1 and Figure 1-1.

Table 1-1: Passing-Bablok Regression and Pearson Correlation of Low-Dose Samples

Comparison	N	R^2	P-B Slope	Slope 95% CI
18 °C vs. 28 °C	48	0.99	1.02	0.98 to 1.07

Figure 1-1: Passing-Bablok Regression of Low-Dose Samples



Conclusion: This analysis resulted in the expected Passing-Bablok slope of 1.0 ± 0.1, and did not replicate the aberrant concordance regression slope as found in the Concordance Study.

Reanalysis 2: During the development phase of the AccuTnI+3 project, BEC conducted a full low-dose concordance/agreement study, following the same protocol as was used in the Submission using 200 native low-dose samples. (See next section for a complete description of that study design). These data were reanalyzed using a Passing-Bablok regression. Results of the reanalysis of the pre-verification concordance study are shown below in Table 1-2, Figure 1-2, and Figure 1-3.

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Table 1-2: Pre-Verification Concordance - Passing-Bablok Regression and Pearson Correlation

Comparison	N	R^2	P-B Slope	Slope 95% CI
18 °C vs. 26 °C	100	0.98	1.08	1.05 to 1.10
20 °C vs. 28 °C	100	0.98	1.00	0.96 to 1.03

Figure 1-2: Passing-Bablok Regression from 18 °C to 26 °C

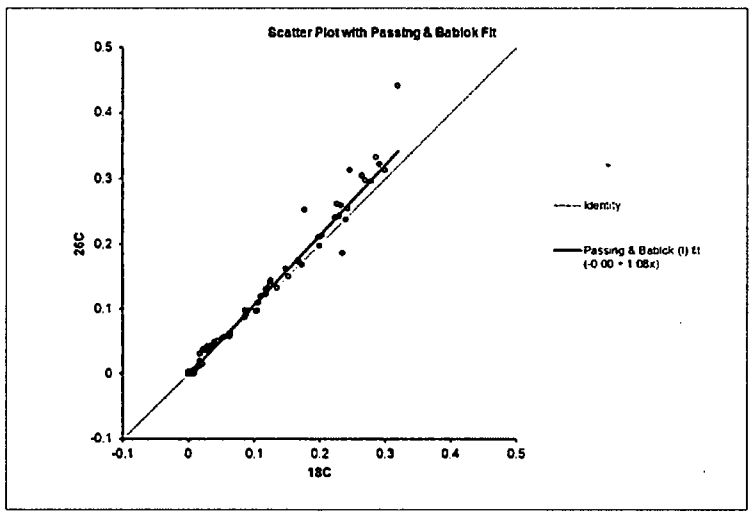
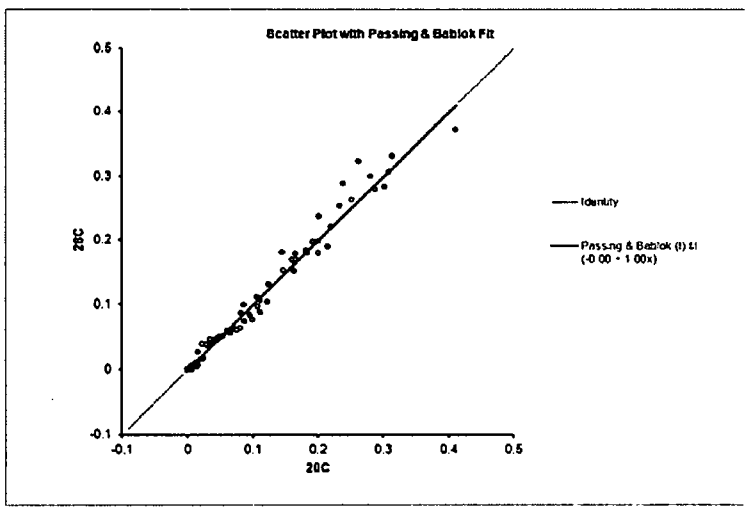


Figure 1-3: Passing-Bablok Regression from 20 °C vs. 28 °C



Conclusion: This analysis resulted in the expected Passing-Bablok slope of 1.0 ± 0.1, and did not replicate the aberrant concordance regression slope as found in the Concordance Study.

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New Studies:

Concordance Repeat Study: BEC repeated the entire Thermal Sensitivity-Impact on Low Dose Concordance/Agreement Study. As the root cause investigation was still in progress, with sample handling as a primary hypothesis of the anomalous results in the submitted study, BEC obtained two hundred and twenty prospectively collected lithium heparin plasma samples that were handled according to the AccuTnI+3 Instructions for Use (IFU). This study followed the original Concordance Study protocol.

Study Description: Two-hundred twenty (220) lithium heparin plasma samples near the clinical cutoff were tested using two reagent pack lots on two Access 2 instruments at six ambient temperature conditions: 18 °C, 20 °C, 22 °C, 24 °C, 26 °C, and 28 °C. Each sample was divided into three aliquots, and tested in duplicate at either 18 ° C, 22 °C, and 26 °C or at 20 °C, 24 °C, and 28 °C.

Data Analysis: Data were analyzed as described in the original Submission, Section 8.13.

A McNemar analysis was performed to determine whether the number of mismatched comparisons was due to random scatter or a systematic difference.

◊ For this analysis, a p-value ≥0.05 represents random variability (non-significant). If p was <0.05 (significant), concordance was evaluated. Bias between low and high temperature was computed using a log-log regression fit.

In addition, to evaluate the impact of temperature using the same method of analysis as the FDA, Pearson Correlation and Passing-Bablok regression were performed on the Low temperature versus High temperature results for each study.

Acceptance Criteria:

◊ From the original study criteria: At the URL of 0.02 ng/mL and the clinical cutoff of 0.03 ng/mL, the McNemar p-value should be non-significant (≥ 0.05). If the p-value is significant, overall concordance must be ≥ 90%.

◊ Added acceptance criteria: If the Pearson correlation $R^2 \geq 0.95$, the Passing-Bablok slope must be 1.00 ± 0.10. If $R^2 < 0.95$, then the bias estimate at the clinical cutoff of 0.03 ng/mL must be ≤0.0084 ng/mL, using a best fit regression line.

The results of the McNemar analysis at 0.02 ng/mL for all comparisons of lower temperature vs. higher temperature are shown below in Table 1-3.

Table 1-3: Thermal Sensitivity/Concordance Results, 0.02 ng/mL cutoff

Analysis	McNemar P-value	% Overall Agreement	% Agreement 95% CI	Bias (ng/mL)	Bias 95% CI
Low vs. High Temp	0.0003	95%	93-96%	0.0034	0.0025 – 0.0043

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The results of the McNemar analysis at 0.03 ng/mL for all comparisons of lower temperature vs. higher temperature are shown below in Table 1-4.

Table 1-4: Thermal Sensitivity/Concordance Results, 0.03 ng/mL cutoff

Analysis	McNemar P-value	% Overall Agreement	% Agreement 95% CI	Bias (ng/mL)	Bias 95% CI
Low vs. High Temp	0.0043	97%	95-98%	0.0035	0.0026 – 0.0045

The results of the Pearson Correlation and Passing-Bablok regressions performed on the low temperature vs. high temperature data for each study are shown below in Table 1-5, Figure 1-4, and Figure 1-5.

Table 1-5: Concordance Study - Passing-Bablok Regression and Pearson Correlation

Comparison	N	R^2	P-B Slope	Slope 95% CI
18 °C vs. 26 °C	110	1.00	0.96	0.93 – 0.98
20 °C vs. 28 °C	110	0.99	0.98	0.95 – 1.00

Figure 1-4: Passing-Bablok Regression from 18 °C vs. 26 °C

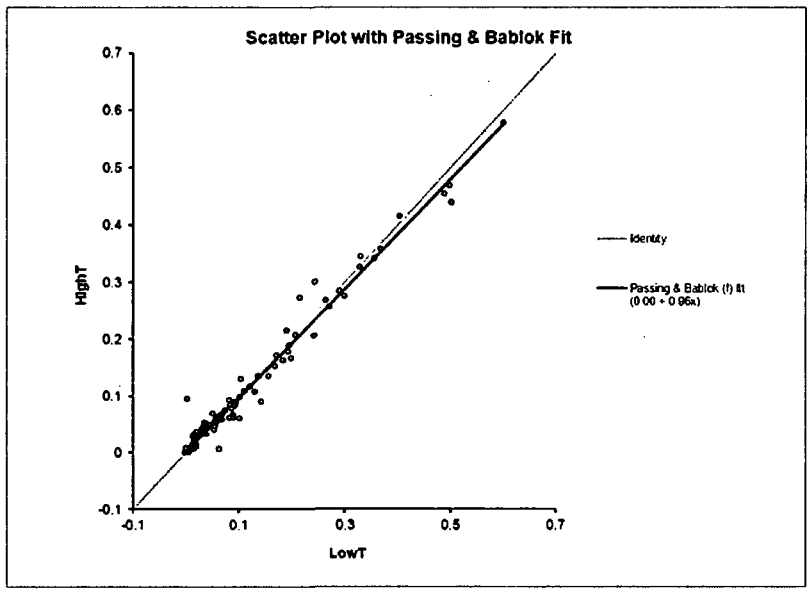

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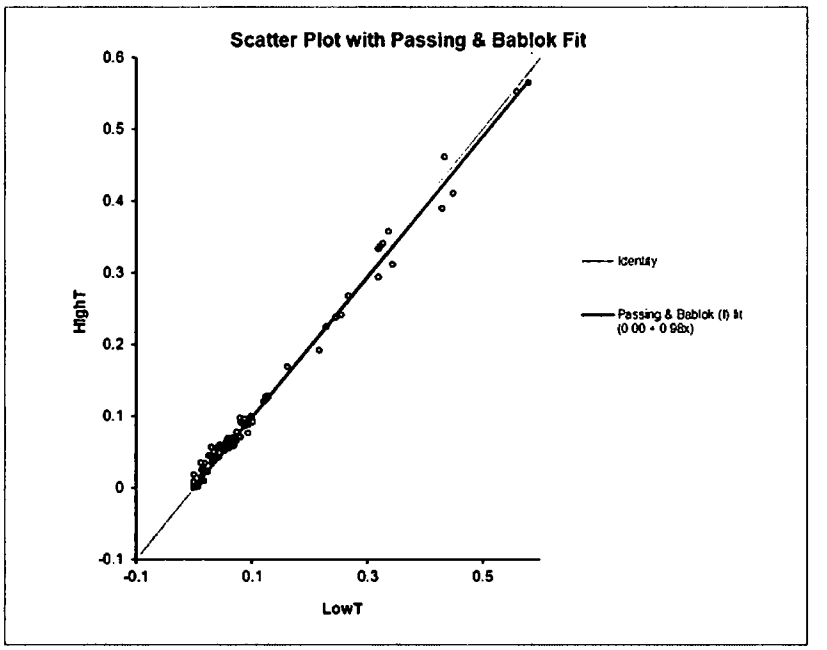
Figure 1-5: Passing-Bablok Regression from 20 °C vs. 28 °C



Conclusion: The repeated Thermal Sensitivity-Impact on Low Dose Concordance/Agreement study meets all original and new acceptance criteria, and does not reproduce the anomalous results in the original Concordance Study.

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In Question 1, FDA observed that the proportion of observations above 0.03 ng/mL varied by temperature as shown below in Table 1-6 and did not believe that the data provided demonstrates concordance across temperatures:

Table 1-6: FDA Proportion Analysis of Original Concordance Study

Temp	18 °C	22 °C	26 °C
% above cutoff	46.4 (51/110)	47.6 (29/82)	55.55 (61/110)
Temp	20 °C	24 °C	28 °C
% above cutoff	42.7 (47/110)	48.1 (53/110)	57.3 (63/110)

BEC performed a similar proportion analysis of the data from the repeated concordance study, and the results of that analysis are shown below in Table 1-7.

Table 1-7: BEC Proportion Analysis of Repeated Concordance Study

Temp	18 °C	22 °C	26 °C
% above cutoff	67.3 (74/110)	65.5 (72/110)	70.9 (78/110)
Temp	20 °C	24 °C	28 °C
% above cutoff	68.2 (75/110)	70.0 (77/110)	70.9 (78/110)

Conclusion: In the repeat concordance study, the proportion of observations above 0.03 ng/mL demonstrates concordance across temperatures, and the temperature trend observed in the anomalous Concordance Study is not reproduced.

Additional Confirmatory Studies:

To further demonstrate that temperature sensitivity of samples containing low concentrations of TnI analyte has been resolved, seven independent confirmatory studies were conducted.

Study Description: For each individual study, a minimum of 40 native lithium heparin plasma samples near the clinical cutoff were tested in duplicate at 18 °C and 28 °C. De-identified, residual plasma samples were obtained from a minimum of five independent external sources.

Data Analysis: A Pearson Correlation and Passing-Bablok regression were performed on the 18 °C vs. 28 °C results for each study.

Acceptance Criteria: If the Pearson Correlation $R^2 \geq 0.95$, the Passing-Bablok slope must be 1.00 ± 0.10. If $R^2 < 0.95$, then the bias estimate at the clinical cutoff of 0.03 ng/mL must be $\leq$ 0.0084 ng/mL, using a best fit regression line.

Results: For the seven independent confirmatory studies, all met the criteria of Pearson Correlation $R^2 \geq 0.95$ and the Passing-Bablok slopes were 1.00 ± 0.10. See Table 1-8 and Figure 1-6, Figure 1-7, Figure 1-8, Figure 1-9, Figure 1-10, Figure 1-11, and Figure 1-12 below.

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Table 1-8: Summary Table for Confirmatory Studies - Passing-Bablok Regression and Pearson Correlation

Confirmatory Study #	Comparison	N	R^2	P-B Slope
1	18 °C vs. 28 °C	50	0.99	0.97
2	18 °C vs. 28 °C	50	1.00	0.92
3	18 °C vs. 28 °C	50	0.99	0.97
4	18 °C vs. 28 °C	50	1.00	0.99
5	18 °C vs. 28 °C	50	1.00	0.90
6	18 °C vs. 28 °C	50	0.99	0.99
7	18 °C vs. 28 °C	133	0.98	0.99

Figure 1-6: Confirmatory Study # 1 - Passing-Bablok Regression

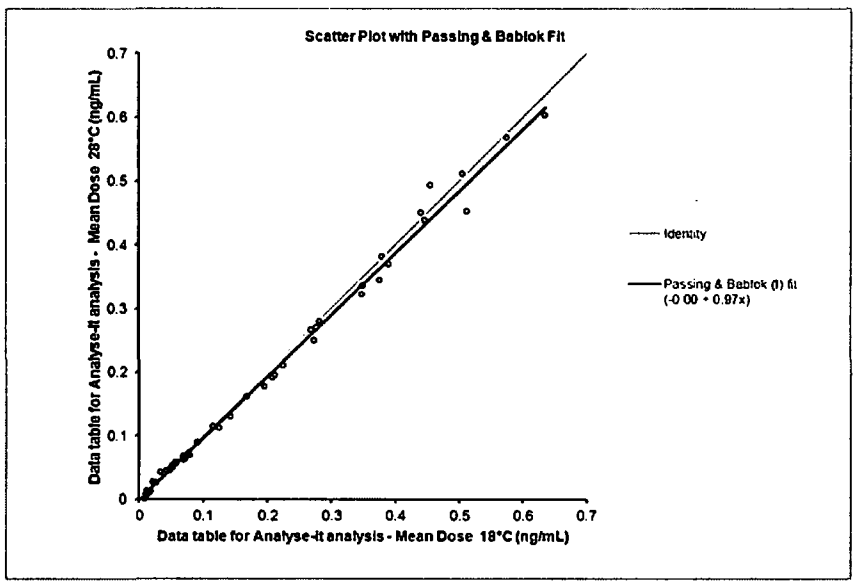

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Figure 1-7: Confirmatory Study # 2 - Passing-Bablok Regression

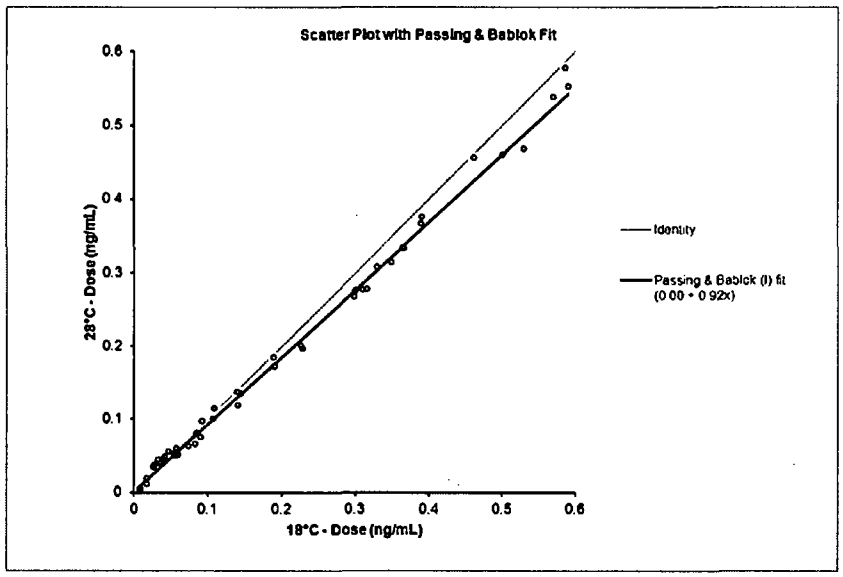

Figure 1-8: Confirmatory Study # 3 - Passing-Bablok Regression

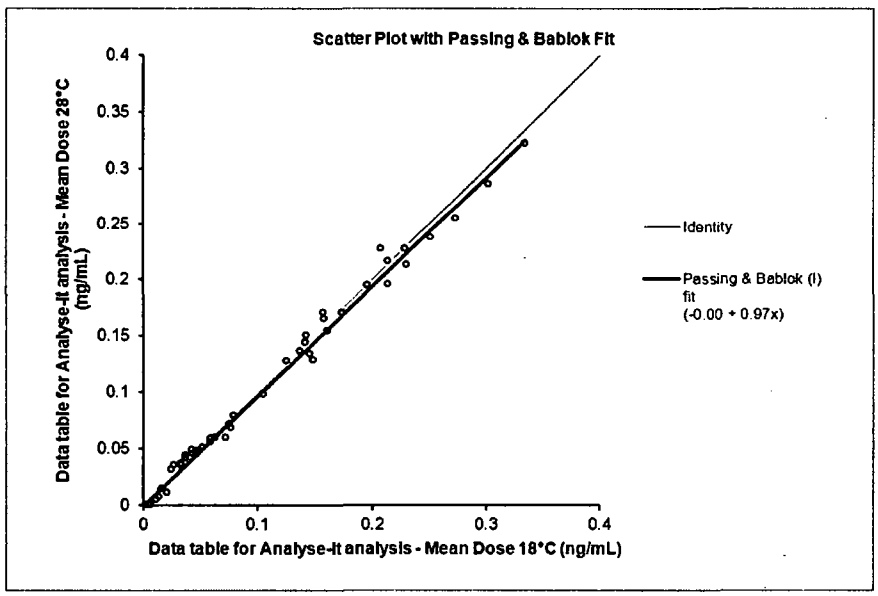

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Figure 1-9: Confirmatory Study # 4 - Passing-Bablok Regression

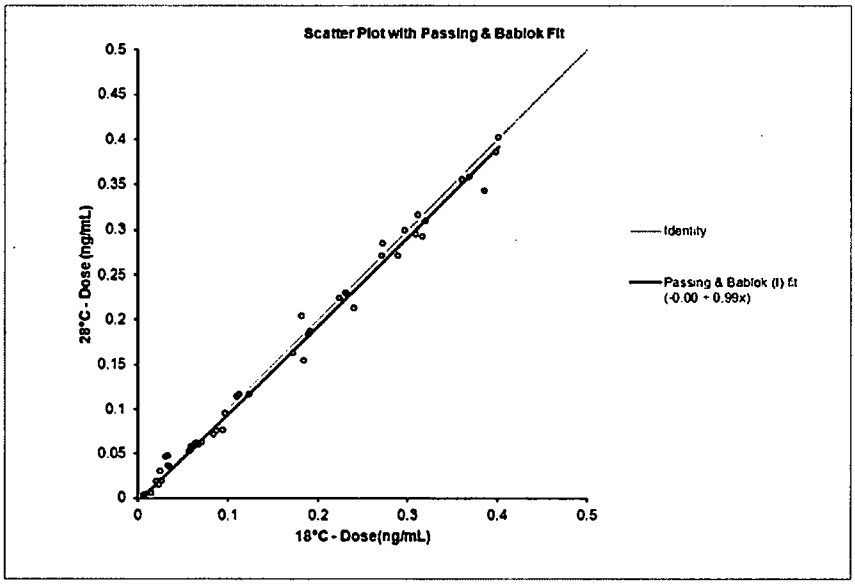

Figure 1-10: Confirmatory Study # 5 - Passing-Bablok Regression

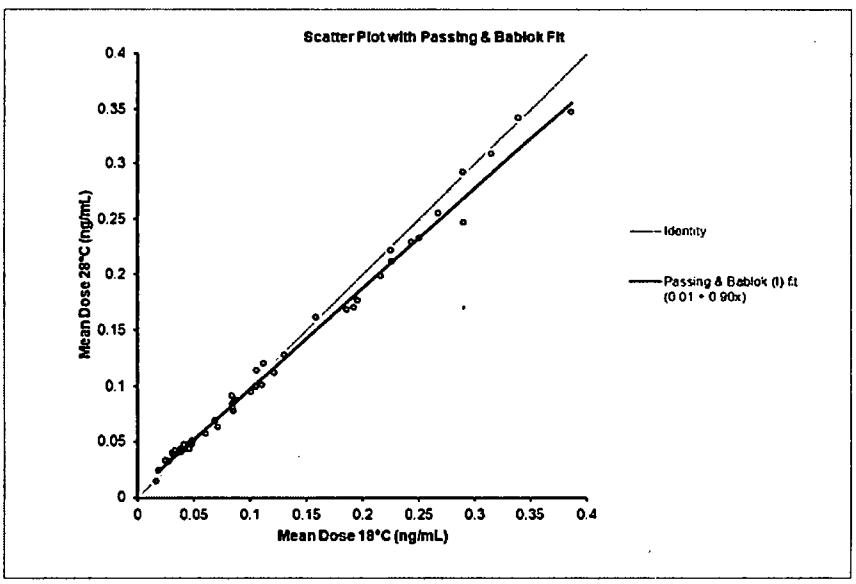

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Figure 1-11: Confirmatory Study # 6 - Passing-Bablok Regression

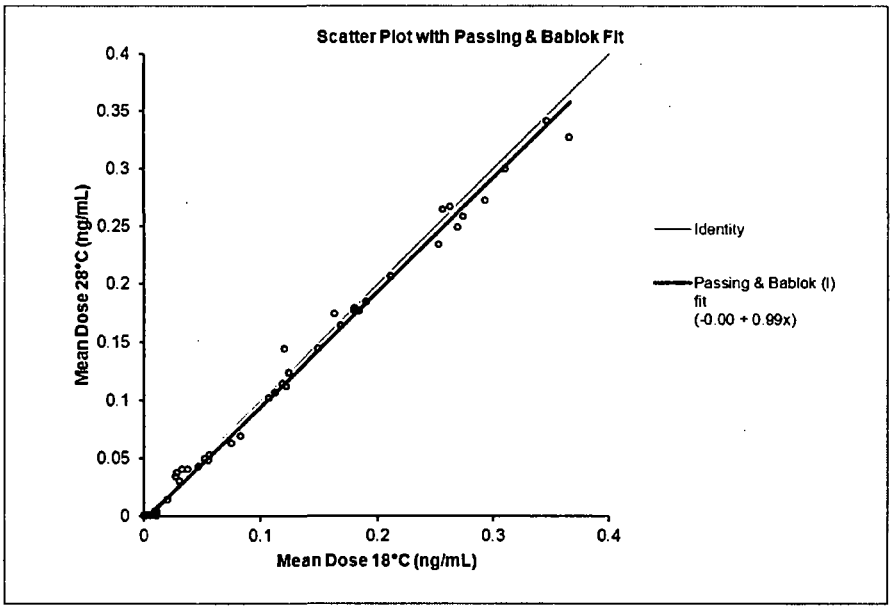
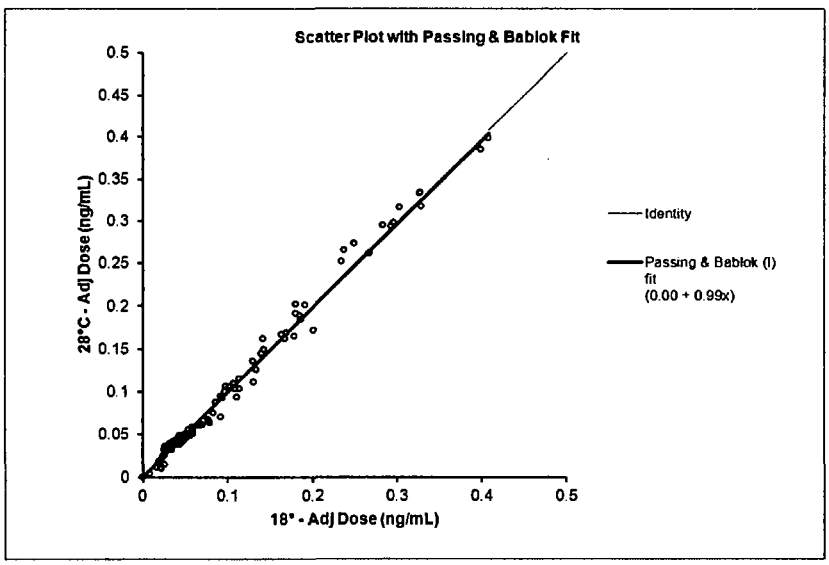


Figure 1-12: Confirmatory Study # 7 - Passing-Bablok Regression



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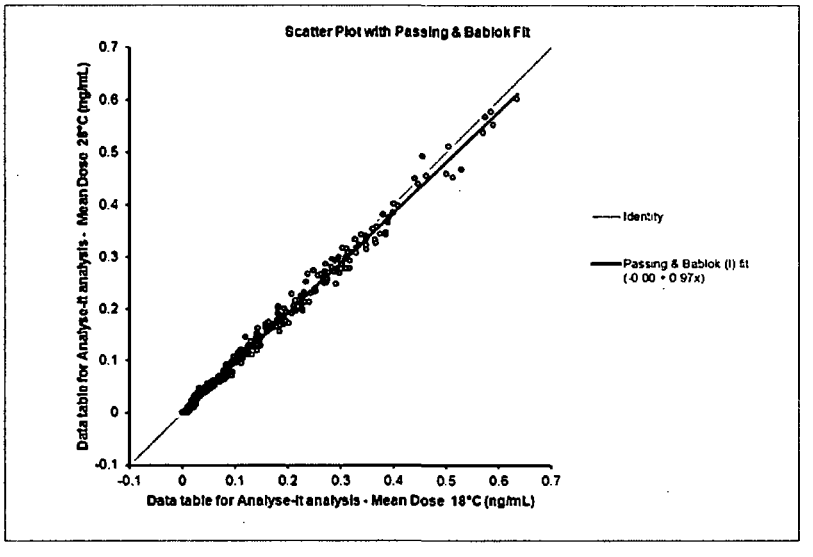
The results from the samples used in the seven confirmatory studies were combined (n = 433) and evaluated together. A two-by-two concordance table was constructed using the 0.02 ng/mL URL and the 0.03 ng/mL clinical cutoff, the McNemar p-values calculated, and the percent agreement determined. The data were also analyzed in total for Passing-Bablok regression and Pearson Correlation. See Table 1-9 and Figure 1-13 below.

Table 1-9: Combined Confirmatory Study - Concordance Results

Analysis at Cutoff	McNemar P-value	% Overall Agreement	R^2	P-B Slope	Slope 95% CI
0.02 ng/mL Low vs High Temp	.0215	98%	0.99	0.97	0.96-0.98
0.03 ng/mL Low vs High Temp	<0.0001	96%			

Figure 1-13: Combined Confirmatory Study - Passing-Bablok Regression and Pearson Correlation



Conclusion: These analyses and results from ten studies and our concordance root cause investigation demonstrate that:

- ◊ There is concordance across temperatures,
- ◊ There is acceptable performance of the device irrespective of ambient temperature,
- ◊ The original concordance study was anomalous, and
  The thermal sensitivity issue has been resolved, and the device is safe and effective for its intended use.

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1.a.ii. FDA: A p-value above 0.05 does not prove that there is no meaningful bias. A more appropriate acceptance criteria would require that the study prove that the level of disagreement between measures taken at difference temperatures be statistically significantly below a pre-specified clinically acceptable level. Confidence intervals (accounting for repeated measures on individual subjects) should be provided for all measures of agreement.

BEC Response to Question 1.a.ii.

BEC has included quantitative measures of acceptable temperature-associated bias in the acceptance criteria, which include the calculation of the bias at the cutoff and the Passing-Bablok regression. Confidence Intervals have been provided in the tables above in our response to Question 1.a.i. for all measures of agreement.

1.b. FDA: Thermal Sensitivity –Robustness: This study used native plasma/serum, spiked plasma/serum and quality control materials at 10 different levels of troponin I, 2 instruments and 6 ambient temperature conditions. Each sample was tested in replicates of 5 on each instrument and at each temperature condition. A calibration curve was established at each temperature condition on each instrument. The individual results were calculated from the calibration curve established at each temperature. A percent difference in the average dose at each temperature compared to the mean dose achieved at 25°C was calculated for each sample and plotted as a function of temperature Your acceptance criteria were that the slope term of each linear fit is either not significant or significant but has an average slope <0.010. Your results met your acceptance criteria since all slopes were significant but had an average slope <0.010. We do not know how to interpret this study since it was not performed as this device is intended to be used. While you claim that the instrument calibration is stable for 56 days (irrespective of ambient temperature), this study was performed by generating a calibration curve at each temperature tested. We are concerned that the test results obtained may be more accurate if the measurement is taken at the same temperature it was calibrated. Furthermore, we do not understand the rationale of your acceptance criteria. Therefore, we are concerned that this study design does not demonstrate that the thermal sensitivity issue has been resolved.

BEC Response to Question 1.b.

Our response to Question 1.b. will

- ◊ Describe the appropriateness of the general study design calibration strategies,
- ◊ Explain how the data from the original studies were reanalyzed to demonstrate that AccuTnI+3 results are accurate irrespective of calibration temperature,
- ◊ Present the outcome of the reanalysis of Thermal Sensitivity-Impact on Thermal Robustness,
- ◊ Discuss the rationale for the acceptance criteria for the slope to be < 0.010. (i.e., acceptance criteria for maximum % change per degree)

General study design calibration strategy:

For the Thermal Sensitivity – Robustness (1b), Thermal Sensitivity – Method Comparison (1c), LOB (5a), LOD (5b), LOQ (5c), and Precision (10) studies, FDA expressed concern that test results may be more accurate if the measurement is taken at the same temperature it was calibrated. In the "K121214 Meeting Briefing Package" dated October 17, 2012 (see Appendix 2), BEC provided details about differences in thermal behavior between the calibrator antigen and native patient samples. The thermal algorithm was designed to address these differences. On November 7, 2012, in a written response to BEC's briefing

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package (see Appendix 3), the Agency restated the need to understand the performance of the device as it is intended to be used. FDA specifically asked BEC to provide data for the requested studies to "demonstrate that the performance of your device is equivalent irrespective of ambient temperature and that your device is safe for patient use."

Further evidence is provided in this Response, to support the fact that the calibration strategy is entirely consistent with how the device is intended to be used, and does not adversely affect the accuracy of the test results. BEC conducted our studies in accordance with the AccuTnI+3 Instructions for Use to the extent consistent with the complexity of the studies and the requirements of the Clinical Laboratory Standards Institute (CLSI) guidelines. During the AccuTnI+3 assay verification testing, a number of calibrations were performed at multiple temperatures throughout the ambient temperature operating range (18 °C - 28 °C) of the Access 2 system to comply with testing guidelines, or as required by our testing protocols.

The device labeling neither requires nor precludes generating calibration curves at the same temperature at which measurements are made. It also does not specify the frequency of calibration, other than it must be performed at a minimum of every 56 days. The AccuTnI+3 assay is designed so the user may calibrate at any temperature within the operating range, and then run the assay at any temperature within that range. BEC developed the calibration strategy for the AccuTnI+3 testing to rigorously evaluate the effect of different ambient temperatures on sample results and calibrator results in any combination. We developed the calibration strategy to prove that the AccuTnI+3 assay:

- May be calibrated at any temperature across the operating range and produce accurate sample test results, and that
- Once calibrated (at any temperature), will produce accurate sample test results regardless of the ambient laboratory temperature at the time the samples are tested.

Data reanalysis:

To demonstrate that the temperature at which the assay is calibrated does not affect the accuracy of the results, BEC conducted additional analyses of original data using multiple calibration curves at various temperatures for the requested studies: Thermal Sensitivity – Robustness (1b), Thermal Sensitivity – Method Comparison (Question 1.c.), LoB (Question 5.a.), LoD (Question 5.b.), LoQ (Question 5.c.), and Precision (Question 10).

We were able to reanalyze these data because the Access 2 instrument stores multiple calibration curves even though only one calibration curve is actively used to calculate test results at any given time. As long as a calibration is within its 56 day expiration dating and is performed on the same instrument for the same reagent lot, we can reanalyze the patient results using any available valid calibration curve on the instrument.

As outlined in Section 3 of the Access 2 Reference Manual, the Access 2 instrument measures calibrator and sample results in relative light units ("RLUs"). The system software uses the RLUs of the calibrators with known concentrations to mathematically calculate the troponin I concentration of samples. We reanalyzed the test results by converting the sample RLUs from a specific temperature set point to a troponin I concentration using the calibration curves generated at different temperature set points. For example, for Method Comparison we reanalyzed sample results generated at 18 °C by converting the RLUs to a troponin I concentration using a calibration curve generated at 24 °C and one at 28 °C. This was done for each calibration temperature and each sample test temperature. Once the data were calculated for all samples, they were compared as follows:

◊ Sample concentrations from 18 °C, 24 °C and 28 °C with a calibration generated at 18 °C.
◊ Sample concentrations from 18 °C, 24 °C and 28 °C with a calibration generated at 24 °C.

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◊ Sample concentrations from 18 °C, 24 °C and 28 °C with a calibration generated at 28 °C.

These analyses confirm that our calibration strategy did not affect the accuracy of the test results. As requested, we are providing data for the requested studies demonstrating the performance of the device as it is intended to be used, in our responses to Questions 1.b., 1.c., 5.a., 5.b., 5.c. and 10 of this Response.

Results of data reanalysis of Thermal Sensitivity-Robustness:

To specifically demonstrate the accuracy of sample results when measurement is taken at a different temperature from which the assay was calibrated, an additional analysis of the Thermal Sensitivity – Robustness study was performed using calibration curves generated at multiple temperature set points as described above. Regardless of calibration temperature, the difference in results meets the acceptance criteria (slope term of each linear fit is either not significant or significant but has an average slope < 0.010) in all cases.

Table 1-10 below lists the calibrations performed at each temperature and the resulting slope, % change per degree Celsius, and bias between the results at either temperature extreme of the ambient temperature range using a regression of the results generated at the six temperature set points. For example, the sample results tested at the six temperature set points had a % change per degree of -0.466% when using the calibration curve generated at 16 °C.

Table 1-10: Thermal Robustness Reanalysis

Calibration Temperature	Slope	% Change/ °C	% Difference 28 °C vs. 18 °C
Combined*	-0.005	-0.511	-5.1
16 °C	-0.005	-0.466	-4.7
19 °C	-0.005	-0.498	-5.0
22 °C	-0.005	-0.504	-5.0
25 °C	-0.005	-0.526	-5.3
27 °C	-0.005	-0.514	-5.1
30 °C	-0.006	-0.554	-5.5

*"Combined" is the data originally included in the Submission Section 8.12, which combined the results obtained at all six of the calibration temperatures shown in the table above.

Conclusion: Regardless of differences between the temperatures at which the device is calibrated and the measurement is taken, the accuracy of the device is maintained within acceptable limits up to and beyond the extremes of the allowed ambient temperature range (18 °C - 28 °C). The percent change per °C is less than 1% in all cases and ranged from -0.466 to -0.554. This additional data analysis demonstrates:

◊ The assay performs as intended, specifically with respect to assay calibration. The calibration strategy of calibrating and testing at the same temperature does not produce results that are more accurate than if sample measurements were taken at different temperatures from which the assay was calibrated.
◊ Calibrations can be performed at any temperature within the operating range of the Access 2 system and accurate sample results will be obtained.
◊ The 56-day stability of the calibration curve was demonstrated in a separate study and is further discussed in our response to Question 18.c.

Acceptance criteria background:

In several sections of the Letter, FDA noted their concerns that the acceptance criteria may be too broad. In our responses to FDA's specific questions, BEC has described the process used to define the acceptance

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criteria and provided the supporting statistical and medical-use rationale. BEC used the acceptance criteria for the current AccuTnI device as the basis for the pre-defined acceptance criteria for all AccuTnI+3 verification studies.

BEC also reviewed information from key opinion leaders, published diagnostic guidelines, internal statistical rationales, and review of the IFUs for cleared troponin devices to refine the design input specifications and acceptance criteria where appropriate.

The intended use of AccuTnI+3 is to aid in the diagnosis of myocardial infarction. Troponin is not the only element used in making a diagnosis of myocardial infarction. However, it plays an integral role. The 2012, Third Universal Definition of Myocardial Infarction[1] notes that a rise and/or fall of cardiac troponin I or troponin T concentrations in serially collected blood samples, with at least one value above the 99th percentile URL and a strong pre-test likelihood, establishes the diagnosis of MI.[2] Since an assay's ability to detect a change in cTn values is dependent on the precision of that assay, assays with better precision at the 99th percentile URL are preferred. The 2012 Universal Definition document considers cardiac troponin assays with CVs less than or equal to 10% at the 99th percentile URL to be optimal. Additionally, the document considers assays with CVs greater than 10% and up to 20% CV at the 99th percentile URL to be acceptable.

Acceptance Criteria for Thermal Sensitivity

The acceptance criterion for thermal sensitivity is ≤ 1% per degree Celsius. By reducing thermal sensitivity from ~3.5% per degree to < 1% per degree, application of the algorithm results in a less than 10% thermally-induced bias over the total 10-degree ambient operating range of the assay (18 °C - 28 °C). This meets the method comparison regression agreement specification of slope = 1.0 ± 0.10.

◊ This is not an additive specification, but embedded within all other acceptance criteria.

- For example, even with the <1% per degree thermal sensitivity, the assay still meets the imprecision criterion of ≤8 % CV.
- Likewise, the method comparison regression criterion of slope = 1.0 ± 0.10 is inclusive of thermal sensitivity, and was verified across the entire ambient temperature range.

◊ In practical use, laboratories rarely encounter a 10°C ambient temperature change during the course of operation. Typical laboratory ambient temperature variance is < 4°C in 24 hours.

◊ This acceptance criterion is consistent with allowable bias goals cited by multiple industry database sources such as Rilibak[4] and Ricos[5].

1.c. *FDA: Thermal Sensitivity-Impact on Cross-Temperature Method Comparison: This study tested 108 lithium heparin plasma patient samples in replicates of 2 at each of 3 temperatures (18°C, 23°C and 28°C ± 2C). The study was run on 2 instruments and 1 reagent lot. Individual sample results were calculated from the calibration curve established at each temperature. These 6 results were averaged to determine the best estimate for each sample at each temperature. Using this best estimate, between-temperature calculation[s] using a Passing-Bablok regression were performed as follows: 23°C vs 18°C, 23°C vs 28°C and 28°C vs 18°C. Your acceptance criteria was that the slope should be 1.00 ± 0.10: r ≥ 0.95. As discussed above in 1b, we do not know how to interpret this study since it was not performed as this device is intended to be used (i.e. generating calibration curves at each temperature is not the labeled procedure for this assay). We are also concerned that your proposed acceptance criteria are too broad for the intent of this testing and ultimately that your study design does not demonstrate that the thermal sensitivity issue has been resolved.*

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BEC Response to Question 1.c.

For the reasons explained above in our response to Question 1.b., the calibrations performed for the Thermal Sensitivity-Impact on Cross-Temperature Method Comparison study are appropriate for the study design. The data below demonstrate that the temperature at which the assay is calibrated does not affect the accuracy of the results and demonstrates that there was no thermal impact when the product was used as intended.

Additional analyses:

To demonstrate the accuracy when sample measurement is taken at a different temperature from which the assay was calibrated, an additional analysis of the Thermal Sensitivity-Impact on Cross-Temperature Method Comparison study was performed. Since calibration curves were produced during the study at each temperature set point, we were able to analyze the method comparison results using a calibration curve established at any one temperature.

This additional analysis evaluates thermal bias of sample results generated at multiple temperatures with a calibration performed at only one temperature. Regardless of calibration temperature, the thermal bias of the results meets acceptance criteria of slope 1.00 ± 0.10, $r \geq 0.95$ in all cases (see Table 1-11 below). Therefore, the thermal bias of the assay is not underestimated by the calibration strategy.

Table 1-11: Thermal Sensitivity Method Comparison Reanalysis

Calibration Temperature (°C)	Sample Temperatures (°C)	n	Slope	r-value
Combined*	18 °C vs. 23 °C	108	1.01	1.00
	18 °C vs. 28 °C	108	0.98	1.00
	23 °C vs. 28 °C	108	0.97	1.00
18 °C	18 °C vs. 23 °C	108	0.99	1.00
	18 °C vs. 28 °C	108	0.97	1.00
	23 °C vs. 28 °C	108	0.97	1.00
23 °C	18 °C vs. 23 °C	108	1.02	1.00
	18 °C vs. 28 °C	108	0.98	1.00
	23 °C vs. 28 °C	108	0.96	1.00
28 °C	18 °C vs. 23 °C	108	1.01	1.00
	18 °C vs. 28 °C	108	1.00	1.00
	23 °C vs. 28 °C	108	0.99	1.00

*"Combined" is the data originally included in the Submission Section 8.14 which combined the results obtained at all three of the calibration temperatures shown in the table above.

To further demonstrate the effectiveness of the thermal algorithm, we compared results before (unadjusted) and after the thermal algorithm (adjusted) was applied in the method comparison study. For this analysis, one calibration at 23 °C was used. See Table 1-12, Figure 1-14, and Figure 1-15 below.

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(b)(4)

[redacted]

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(b)(4)

[redacted]

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1.d. FDA: We are concerned that the criteria of ± 2°C for your temperature studies may be too broad for your thermal sensitivity studies. We recommend that you tighten this criteria for any new studies you perform.

BEC Response to Question 1.d.

The criterion of ± 2 °C for our temperature studies is a set point prerequisite and not an acceptance criterion. A thermal environment specification of ± 2 °C from the target temperature set point was used for all thermal sensitivity studies. To further clarify:

◊ The temperature control capability of rooms and chambers large enough to house our instruments required consideration in determining the temperature set points. Current technology for such stringent control of temperature for large rooms precluded establishing a smaller range requirement around any given temperature set point.

◊ To conduct the required multiple temperature studies, BEC installed several thermally controlled environmental rooms and chambers. The capability of the temperature control of these facilities range from ± 1 °C to ± 2 °C depending on the room/chamber size, HVAC system, and the number of systems and amount of heat generated by the equipment in the room.

◊ Small variations in air temperature are expected, but they do not adversely affect study results because the internal temperature of the instrument is the parameter that most critically affects the performance of the assay. Furthermore, such variations simulate the typical variation found in most clinical laboratories and thus represents the environment in which the device is intended to be used.

◊ Ambient temperatures achieved during study execution were fully verified. In the majority of cases, the actual deviation from the target set point temperature was much less than ± 2 °C. Specifically, more than 88% of verified temperatures were within 1 °C of the target temperature for those studies described in the Submission.

◊ The full ambient temperature range (i.e., 18 °C - 28 °C) is represented in the studies that were intended to challenge the extreme boundaries of the device. In addition, in Section 8.12 of the Submission, the study titled Thermal Sensitivity-Robustness included temperature set points beyond the operating range, at 16 °C ±1 °C and 30 °C ±1 °C, assuring algorithm effectiveness up to and beyond the recommended temperature range of 18 °C - 28 °C.

◊ Figure 1-16 and Figure 1-17 below illustrate the distribution of the fully verified temperature ranges for the thermal studies presented in the Submission.

- Each count in the histogram represents the difference between the ambient temperature measured during a study and the target set point.
- For the studies discussed in our responses to Questions 1.d., 5.e., 6.d., 8.g., 9., 10., and 12. for measures of accuracy, precision, and other performance criteria, we have controlled ambient temperatures to the required specifications.

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Figure 1-16: Distribution of Verified Temperature Set Points as °C From Target Temperature

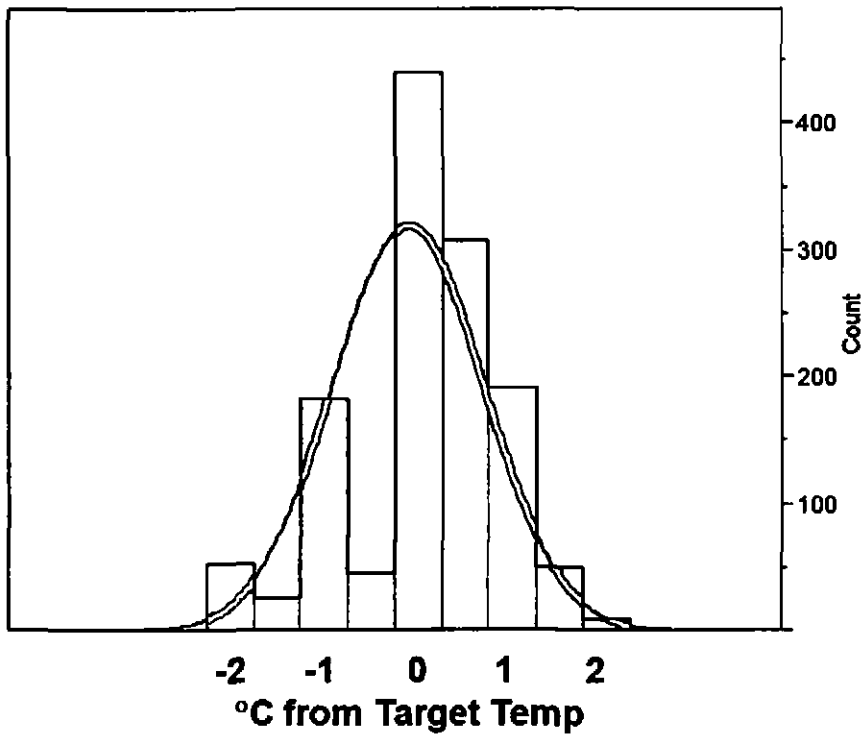

Figure 1-17: Statistics for Figure 1-16

Moments	
Mean	0.129526
Std Dev	0.8041871
Std Err Mean	0.0224165
Upper 95% Mean	0.173503
Lower 95% Mean	0.0855491
N	1287

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Question 2: Intended use

FDA: Your current intended use is "[t]he Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increase probability of ischemic events requiring urgent revascularization procedures." We have the following concerns/recommendations:

2.a. *FDA: You have not provided data from a clinical study demonstrating that this assay aids in the stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increase probability of ischemic events requiring urgent revascularization procedures. As we discussed under pre-IDE I100255, a risk prediction claim will require additional studies. Therefore, at this time, it seems that you do not have evidence to support a prognostic claim. We recommend that you remove the prognosis claim from your intended use statement.*

BEC Response to Question 2.a.

We have removed the risk stratification claim from our intended use statement. The revised intended use statement for Access AccuTnI+3 on the Access 2 Immunoassay Systems is:

> "The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction."

The AccuTnI+3 Instructions for Use has been updated accordingly and is provided with this Response in Appendix 9 and in the revised 510(k) summary in Appendix 12.

2.b. *FDA: Since we are not sure that the matrix comparison studies provided demonstrate that the lithium heparin plasma test results and the serum test results are identical, you may not be able to support your claim that this device can be used on both serum and lithium heparin plasma samples (see item 4). Please amend your intended use if necessary.*

BEC Response to Question 2.b.

In our Submission, BEC has demonstrated a high degree of agreement in correlation, concordance, lack of bias, and equivalent diagnostic efficacy between serum and lithium heparin plasma for specimens both near the clinical cut-off and at higher levels.

The high degree of agreement observed in the serum-plasma matrix comparison study conducted as part of the pivotal clinical trial was confirmed by the results of our internal analytical matrix comparison studies described in the Submission. The data demonstrate the equivalence of the two sample matrices, and the claim for both serum and plasma should be retained in our statement of intended use. The comparison study was conducted using guidance from CLSI EP9-A2, "Method Comparison and Bias Estimation Using Patient Samples: Approved Guideline-Second Edition." Please refer to our responses to Question 4 and Question 12 for additional supporting information.

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Question 3: Pivotal Clinical Trial

FDA: Please provide the following information regarding your clinical study:

3.a. FDA: Poolability of investigation site data: Please address the following:

3.a.i. FDA: On page 60, you examine whether AUC varies by site. Please explain what measurements were included in this analysis. That is, were all samples included? One sample per subject? You offer that you obtained a p-value of at least 0.19 but do not explain what hypothesis was tested. Please provide this hypothesis. Without knowing what hypothesis was tested on what data, FDA cannot assess the validity of your finding.

BEC Response to Question 3.a.i.

For determination of which measurements are included in the analysis, refer to page 54 of the submission: "N's do not add to the total number of subjects due to serial draws - with samples from a single subject in multiple time intervals. If more than one draw was obtained for a particular subject within any specific time interval, the analysis included only one sample per subject per time interval. Thus, a single subject can appear in multiple time intervals but no more than once in each time interval."

The Poolability analysis included only one sample per subject per time interval. When multiple samples were collected from the same subject within the same time interval, the second draw was used in the analysis, which reflects how this device would be used in clinical practice, i.e., if the first draw was not clinically definitive, additional draw(s) were requested until a diagnosis could be determined. Additional discussion of this topic is provided in our response to Question 3.b.i.

Poolability across sites was evaluated by testing whether the AUCs differed by site using the general parametric approach for testing heterogeneity described by Whitehead and Whitehead (Ref: Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med.1991). The null hypothesis was:

$$H_0: AUC_1 = AUC_2 = \ldots = AUC_{10} = AUC$$

where AUC_x denotes the AUC at each site (except for the AUCs of 1,9,12,15 and 16 which were combined due to small sample size). Under this null hypothesis, the Q statistic was derived and assumed to follow a $\chi 2$ distribution with 9 degrees of freedom, which resulted in a p-value of 0.19.

3.a.ii. FDA: To further justify pooling by site for the efficacy analysis, please provide FDA with a calculation of the proportion of subjects with MI by site, with 95% confidence intervals. Pease also provide estimates of sensitivity and specificity, by time from onset of symptoms, with 95% confidence intervals. Please perform the same analysis by time from hospital admission.

BEC Response to Question 3.a.ii.

Table 3-1 below shows the proportion of subjects with MI by site. We have added a fourth column to the original table presented on pages 46-47 of the Submission to show 95% confidence intervals.

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Table 3-1: MI Incidence by Site

MI Incidence by Site			
Site	# of MIs/# of Subjects	MI Incidence (%)	95% CI
01	6/59	10.2%	3.8 - 20.8
02	32/155	20.6%	14.6 - 27.9
04	35/241	14.5%	10.3 - 19.6
06	34/327	10.4%	7.3 - 14.2
07	26/269	9.7%	6.4 - 13.8
08	19/196	9.7%	5.9 - 14.7
09	1/34	2.9%	0.1 - 15.3
10	17/131	13.0%	7.7 - 20.0
11	23/158	14.6%	9.5 - 21.0
12	8/60	13.3%	5.9 - 24.6
13	20/97	20.6%	13.1 - 30.0
14	22/123	17.9%	11.6 - 25.8
15	0/4	0.0%	0.0 - 60.2
16	10/75	13.3%	6.6 - 23.2
Total	253/1929	13.1%	11.6 - 14.7

We have not provided estimates of sensitivity and specificity (by time from symptom onset or admission) because a minimum of 73 MIs are required to assess cutoffs at 95% sensitivity, and 139 MIs are required to assess cutoffs at 90% sensitivity (Statistical Sample Size Assumptions and Calculations, pages 41-42 of the Submission, and aligned with our May 2010 pre-IDE). The number of MIs per site ranged from 0 to 35 as shown in the table above, and the numbers are smaller still when segmented further by individual time intervals from admission and symptom onset.

CLSI Guideline I/LA21-A2: "Clinical Evaluation of Immunoassays; Approved Guideline - Second Edition" recommends as a minimum guideline at least 50 positive results and 50 negative results to yield sensitivity and specificity estimates with a confidence interval spread of 20 percentage points. An even wider CI spread than 20 is obtained for estimates of sensitivity and specificity by site by time from onset of symptoms and by time from hospital admission, since the number of positive events (MIs) becomes increasingly small. That is, the analysis is not sufficiently powered to evaluate individual sites or detect statistical differences between sites.

In contrast, AUC analysis (page 60 of the Submission) provides an estimate of TnI diagnostic efficacy at each individual site taking all subjects (MI and non-MI) enrolled at each site into account in a single analysis. AUC analysis demonstrated equivalent diagnostic efficacy across sites (Submission Page 60: AUCs ranged from 0.94 to 0.99 for individual sites).

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3.b. FDA: Diagnostic sensitivity and specificity by time after symptom onset: Please provide the following:

3.b.i. FDA: When a subject has more than 1 measurement <8 or ≥8 hours following the onset of symptoms, only 1 measurement is used in the analysis. How is it determined which measurement is included? Ideally, all available observations should be included in the analysis with adjustments made to account for the correlation between repeat measurements made on individual subjects. See Emir et al's 1998 paper in Statistics in Medicine "Analysis of repeated markers used to predict progression of cancer". Please discuss how your analysis reflects how this device will be used and how you will demonstrate the clinical performance of your device in an unbiased manner.

BEC Response to Question 3.b.i.

For determination of which measurements are included in the analysis, refer to page 54 of the submission: "N's do not add to the total number of subjects due to serial draws - with samples from a single subject in multiple time intervals. If more than one draw was obtained for a particular subject within any specific time interval, the analysis included only one sample per subject per time interval. Thus, a single subject can appear in multiple time intervals but no more than once in each time interval."

All study analyses of time intervals, whether time from symptom onset or time from admission, included only one sample per subject per time interval. When multiple samples were collected from the same subject within the same time interval, the second draw was used in the analysis, which reflects how this device would be used in clinical practice, i.e., if the first draw was not clinically definitive, additional draw(s) were requested until a diagnosis could be determined. For the time from admission analysis, no patients had more than two draws in the same time interval. For the time from symptom onset analysis, the time intervals were longer; we used the same second draw rule to be consistent across all analyses.

For some analytes, repeated measures analyses (e.g., Emir et al) using all observations for an individual subject are appropriate; for this analyte, this type of analysis is not appropriate because it does not reflect clinical practice. For clinical assessment, serial draws are obtained until a diagnosis is made, as described in the Universal Definition of MI and in the American College of Emergency Physicians (ACEP) guidelines. Unlike the Emir cancer-progression population, in the chest-pain population, clinical context determines frequency, timing and number of draws, which correlate to clarity of diagnosis (definitive vs. equivocal). The latest draw by definition sets the diagnosis; draws are discontinued immediately in a fast-paced ED setting. Thus, the analysis performed in the submission reflects how this device is used in clinical practice, with each time interval reflecting performance characteristics in an unbiased manner.

3.b.ii. FDA: Some clinicians may also want to see performance characteristic at <12 hours and ≥12 hours after symptom onset. Please provide this analysis if available.

BEC Response to Question 3.b.ii.

As illustrated in Table 3-2 and Table 3-3 below, performance characteristics at ≥ 12 hours are very similar to results at ≥ 8 hours. The same is true for performance characteristics at < 12 and < 8 hours.

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Table 3-2: Results by Time After Symptom Onset

Results ≥ 8 Hours After Symptom Onset

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	96.9	154/159	94.1 - 99.6	81.7	909/1113	79.4 - 83.9
0.03	94.3	150/159	90.7 - 97.9	86.8	966/1113	84.8 - 88.8
0.04	88.1	140/159	83.0 - 93.1	92.7	1032/1113	91.2 - 94.2
0.05	79.2	126/159	72.9 - 85.5	94.9	1056/1113	93.6 - 96.2
0.06	73.0	116/159	66.1 - 79.9	96.3	1072/1113	95.2 - 97.4

Results ≥ 12 Hours After Symptom Onset

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	97.0	98/101	93.7 - 100.0	82.0	583/711	79.2 - 84.8
0.03	95.0	96/101	90.8 - 99.3	86.8	617/711	84.3 - 89.3
0.04	85.1	86/101	78.2 - 92.1	92.3	656/711	90.3 - 94.2
0.05	78.2	79/101	70.2 - 86.3	94.9	675/711	93.3 - 96.5
0.06	72.3	73/101	63.5 - 81.0	96.6	687/711	95.3 - 98.0

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Table 3-3: Results by Time after Symptom Onset (Cont.)

Results < 8 Hours After Symptom Onset

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	96.4	159/165	93.5 - 99.2	83.2	826/993	80.9 - 85.5
0.03	91.5	151/165	87.3 - 95.8	89.1	885/993	87.2 - 91.1
0.04	85.5	141/165	80.1 - 90.8	93.6	929/993	92.0 - 95.1
0.05	78.2	129/165	71.9 - 84.5	95.5	948/993	94.2 - 96.8
0.06	72.7	120/165	65.9 - 79.5	96.9	962/993	95.8 - 98.0

Results < 12 Hours After Symptom Onset

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	96.8	179/185	94.2 - 99.3	83.5	943/1130	81.3 - 85.6
0.03	91.9	170/185	88.0 - 95.8	89.4	1010/1130	87.6 - 91.2
0.04	87.6	162/185	82.8 - 92.3	93.7	1059/1130	92.3 - 95.1
0.05	78.9	146/185	73.0 - 84.8	95.6	1080/1130	94.4 - 96.8
0.06	74.1	137/185	67.7 - 80.4	97.1	1097/1130	96.1 - 98.1

3.c. Diagnostic sensitivity and specificity by time after admission: Please address the following:

3.c.i. FDA: When a subject has more than 1 observation in a given interval, were all observations included or only 1? According to our review of your data there were at least 60 cases in which a subject had more than 1 draw in a given interval. If all were included, you should adjust the analysis to account for correlation between those observations. If only 1 was included, please explain how the measurement used in the analysis was chosen. Please discuss how your analysis reflects how this device will be used and how you will demonstrate the clinical performance of your device in an unbiased manner.

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BEC Response to Question 3.c.i.

Please refer to our response to Question 3.b.i.

3.c.ii. FDA: According to the line data, all 1929 subjects have draws at time zero. There are 21 additional draws occurring between 0.1 and 0.9 hours after baseline. Are these 21 draws not included in the analyses? Are the 70 draws that occurred exactly 3 hours after baseline considered to be in the 1-3 or 3-6 bin? Similarly are the 38 draws that occurred at exactly 6 hours in the 3-6 hour bin or the 6-9 hour bin? There are another 70 draws taken more than 9 hours after baseline. Are these excluded from analyses?

BEC Response to Question 3.c.ii.

The 21 draws were analyzed as described in our response to Question 3.b.i. The measurements included in the analysis reflect the clinical utility of the AccuTnI assay at a single time-point during a particular interval. When multiple samples were collected from the same subject within the same time interval (0-0.9 hours), the second draw was used in the analysis, which reflects how this device would be used in clinical practice, i.e., if the first draw was not clinically definitive, additional draw(s) were requested until a diagnosis could be determined.

The 70 and 38 draws at exactly 3 hours and 6 hours respectively were analyzed as follows:

◊ Draws exactly at 3 hours are included in the 3-6 hour bin.
◊ Draws exactly at 6 hours are included in the 6-9 hour bin.

The 70 draws taken ≥ 9 hours after baseline were not included in the "Time from Admission" analysis for the following reasons:

◊ Only 17 of the 253 MI subjects and 48 of the 1676 non-MI subjects had draws taken in this time interval. The reason is because the majority of MI subjects have received therapy prior to this time interval: the "door-to-balloon time" (the time it takes for a hospital to treat a heart attack patient after he or she arrives at the hospital) recommended by the AHA is 90 minutes. In addition, the majority of non-MI subjects have been ruled-out for MI and discharged prior to this late time interval.
◊ As only 17 MI's and 48 non-MI's remain in this time interval, it is not sufficiently powered to accurately evaluate sensitivity and specificity; a minimum of 73 MI's are required to assess cutoffs at 95% sensitivity, and 139 MI's are required to assess cutoffs at 90% sensitivity (Statistical Sample Size Assumptions and Calculations, pages 41-42 of the submission).

3.d. FDA: Confidence internal analysis: Particularly for smaller samples and for estimates of proportions close to 1, the Wald confidence intervals offer less accurate results than exact confidence intervals. For example, the 95% CI for sensitivity at 6-9 hours is [77.9 – 97.4] using the exact method. This is noticeably lower than the [82.0 – 99.4] that you calculated using Wald. Please repeat and report your analysis using exact confidence intervals for all confidence intervals regarding proportions.

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BEC Response to Question 3.d.

Confidence intervals were calculated in accordance with the pre-IDE clinical plan, the clinical trial protocol (73 MIs for 95±5% sensitivity, 139 MIs for 90±5% sensitivity), and as recommended in CLSI Guideline EP24-A2: "Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves."

However, we have recalculated confidence intervals using the Exact method and have presented them next to the Wald CIs in Table 3-4 and Table 3-5 below. Confidence intervals are similar for both methods for the majority of points, and both calculation methods demonstrate strong sensitivity and specificity results.

Table 3-4: 95% Sensitivity and Specificity Confidence Intervals by Exact and Wald Methods

Baseline								
	Sensitivity				Specificity			
TnI cutoff (≥) ng/mL	%	n/N	Exact 95% CI	Wald 95% CI	%	n/N	Exact 95% CI	Wald 95% CI
0.02	92.1	233/253	88.1 - 95.1	88.8 - 95.4	84.3	1412/1675	82.5 - 86.0	82.6 - 86.0
0.03	87.4	221/253	82.6 - 91.2	83.3 - 91.5	89.3	1495/1675	87.7 - 90.7	87.8 - 90.7
0.04	77.1	195/253	71.4 - 82.1	71.9 - 82.3	93.9	1572/1675	92.6 - 95.0	92.7 - 95.0
0.05	65.6	166/253	59.4 - 71.5	59.8 - 71.5	95.6	1602/1675	94.6 - 96.6	94.7 - 96.6
0.06	59.7	151/253	53.4 - 65.8	53.6 - 65.7	97.0	1625/1675	96.1 - 97.8	96.2 - 97.8

≥ 1-3 Hours								
	Sensitivity				Specificity			
TnI cutoff (≥) ng/mL	%	n/N	Exact 95% CI	Wald 95% CI	%	n/N	Exact 95% CI	Wald 95% CI
0.02	98.4	122/124	94.3 - 99.8	96.2 - 100.0	85.5	867/1014	83.2 - 87.6	83.3 - 87.7
0.03	96.0	119/124	90.8 - 98.7	92.5 - 99.4	89.4	907/1014	87.4 - 91.3	87.6 - 91.3
0.04	89.5	111/124	82.7 - 94.3	84.1 - 94.9	93.5	948/1014	91.8 - 94.9	92.0 - 95.0
0.05	80.6	100/124	72.6 - 87.2	73.7 - 87.6	95.8	971/1014	94.3 - 96.9	94.5 - 97.0
0.06	74.2	92/124	65.6 - 81.6	66.5 - 81.9	97.0	984/1014	95.8 - 98.0	96.0 - 98.1

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Table 3-5: 95% Sensitivity and Specificity Confidence Intervals by Exact and Wald Methods (Cont.)

≥ 3-6 Hours								
	Sensitivity				Specificity			
TnI cutoff (≥) ng/mL	%	n/N	Exact 95% CI	Wald 95% CI	%	n/N	Exact 95% CI	Wald 95% CI
0.02	98.1	154/157	94.5 - 99.6	96.0 - 100.0	81.0	762/941	78.3 - 83.4	78.5 - 83.5
0.03	94.9	149/157	90.2 - 97.8	91.5 - 98.3	86.7	816/941	84.4 - 88.8	84.6 - 88.9
0.04	87.3	137/157	81.0 - 92.0	82.1 - 92.5	93.0	875/941	91.2 - 94.5	91.4 - 94.6
0.05	79.0	124/157	71.8 - 85.1	72.6 - 85.4	95.0	894/941	93.4 - 96.3	93.6 - 96.4
0.06	72.0	113/157	64.3 - 78.8	65.0 - 79.0	96.4	907/941	95.0 - 97.5	95.2 - 97.6

≥ 6-9 Hours								
	Sensitivity				Specificity			
TnI cutoff (≥) ng/mL	%	n/N	Exact 95% CI	Wald 95% CI	%	n/N	Exact 95% CI	Wald 95% CI
0.02	93.0	40/43	80.9 - 98.5	85.4 - 100.0	76.4	188/246	70.6 - 81.6	71.1 - 81.7
0.03	90.7	39/43	77.9 - 97.4	82.0 - 99.4	87.0	214/246	82.1 - 90.9	82.8 - 91.2
0.04	90.7	39/43	77.9 - 97.4	82.0 - 99.4	93.1	229/246	89.2 - 95.9	89.9 - 96.3
0.05	86.0	37/43	72.1 - 94.7	75.7 - 96.4	94.7	233/246	91.1 - 97.2	91.9 - 97.5
0.06	79.1	34/43	64.0 - 90.0	66.9 - 91.2	95.9	236/246	92.7 - 98.0	93.5 - 98.4

3.e. *FDA: Inclusion criteria: You included patient presenting to the emergency room with chest pains occurring "at rest." What is your definition of "at rest"? Did you exclude patients presenting with chest pains following exercise or other stressful situations? If so, please justify why the exclusion of these patients did not bias the results from your clinical study and why you believe these patients are not part of the intended use population of your device.*

BEC Response to Question 3.e.

All patients presenting to the ED with chest discomfort suggestive of ACS and consistent with myocardial ischemia were enrolled in the trial (intended use population, "all-comers").

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This included patients presenting with chest pain following exertion or stressful situations, as well as patients presenting with ischemic symptoms occurring at rest (defined as no or minimal activity).

The study did not exclude patients presenting with chest pain following exercise or other stressful situations.

3.f. FDA: Instrument calibration: Please describe the frequency at which the testing laboratories calibrated each instruments while they were determining the troponin results for the pivotal clinical trial, the matrix comparison trial and the reference interval trial.

BEC Response to Question 3.f.

At each clinical study testing site, calibration was performed on each reagent lot prior to the initiation of testing. Per the clinical testing protocol, two sets of commercial tri-level quality controls (QC) were tested each day before study specimens were tested. Once the QC were confirmed to be within the expected ranges, study testing was begun. Following the protocol, the sites recalibrated approximately monthly or as required for troubleshooting (e.g., if QC fell out of range). Dates of calibration and testing dates are described in Table 3-6 below:

Table 3-6: Calibration and Study Testing Dates

Site #		Calibration Date(s)		Study Testing Dates		
	Reagent Lot	Initial Calibration	Subsequent Calibrations	Study	Testing Start	Testing End
1	Lot 1	12/7/2011	1/10/2012	Pivotal	12/22/2011	2/14/2012
	Lot 2	12/7/2011	2/2/2012	Reference Interval	1/19/2012	1/19/2012
	Lot 3	12/7/2011	1/19/2012	Matrix Comparison	12/22/2011	1/31/2012
2	Lot 2	1/18/2012	n/a	Reference Interval	1/19/2012	1/27/2012
3	Lot 1	12/6/2011	2/3/2012	Pivotal	12/20/2011	2/28/2012
	Lot 2	12/6/2011	1/23/2012	Reference Interval	1/19/2012	1/20/2012
	Lot 3	12/6/2011	1/9/2012 1/11/2012	Matrix Comparison	12/21/2011	2/8/2012
4	Lot 1	12/9/2011	1/25/2012	Pivotal	12/22/2011	2/8/2012
	Lot 2	12/9/2011	2/2/2012	Matrix Comparison	12/24/2011	12/30/2011
	Lot 3	12/9/2011	1/9/2012			
5	Lot 1	12/8/2011	2/8/2012	Pivotal	1/11/2012	2/8/2012

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Question 4: Clinical matrix comparison study

FDA: You compared lithium heparin plasma and serum using native patient samples randomly selected from among the entire pivotal trial cohort. Lithium heparin plasma and serum results were determined on the Access 2 Instrument in singlet, using 3 lots of reagents. A total of 107 matched samples were included in this analysis. You provided Passing Bablok regression analysis for samples ranging from 0.01 to 20 ng/mL and for the subset of samples within the 107 samples that ranged from 0.01 to 5 ng/mL. The results are as follow:

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.01 – 20	107	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00
0.01 – 5	104	1.00 (1.00 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00

You concluded that excellent agreement was observed and that these results are similar to those reported in the analytical performance section. However, in the points to consider for Troponin 510(k) submission provided to you under pre-IDE I100255 we recommended that as part of your pivotal clinical study, you collect and test specimens for each claimed sample matrix to obtain clearance for multiple matrices. We still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) when serum samples are used at the pre-specified cut-offs.

BEC Response to Question 4

BEC conducted the matrix comparison study consistent with the recommendations of FDA, as discussed in the e-mail correspondence between Dr. Kurtis Bray (BEC) and Dr. Ileana Elder (FDA). These e-mails are attached in Appendix 5. In that correspondence with the Agency, BEC had specifically requested clarification about requirements for validation of additional matrix types through a matrix comparison study.

As part of our clinical performance evaluation and pursuant to Dr. Elder's advice, BEC performed a serum and lithium heparin plasma sample matrix comparison study. Following Dr. Elder's guidance, we demonstrated that there is little to no bias between the serum and lithium heparin plasma specimens (n=123 pairs) whose TnI levels spanned the assay range.

Analytical agreement between the two specimen types was originally evaluated by Passing-Bablok regression analysis of results from the 107 subjects whose TnI levels were above 0.01 ng/ml. The excellent agreement shown between the matrices for specimens from the pivotal study as documented in the Submission (n = 107, slope = 1.00, 95% CI= 0.98 – 1.00, Y intercept = 0.00, r = 1.00) demonstrated the equivalence of serum to plasma as sample matrices for the AccuTnI+3 assay.

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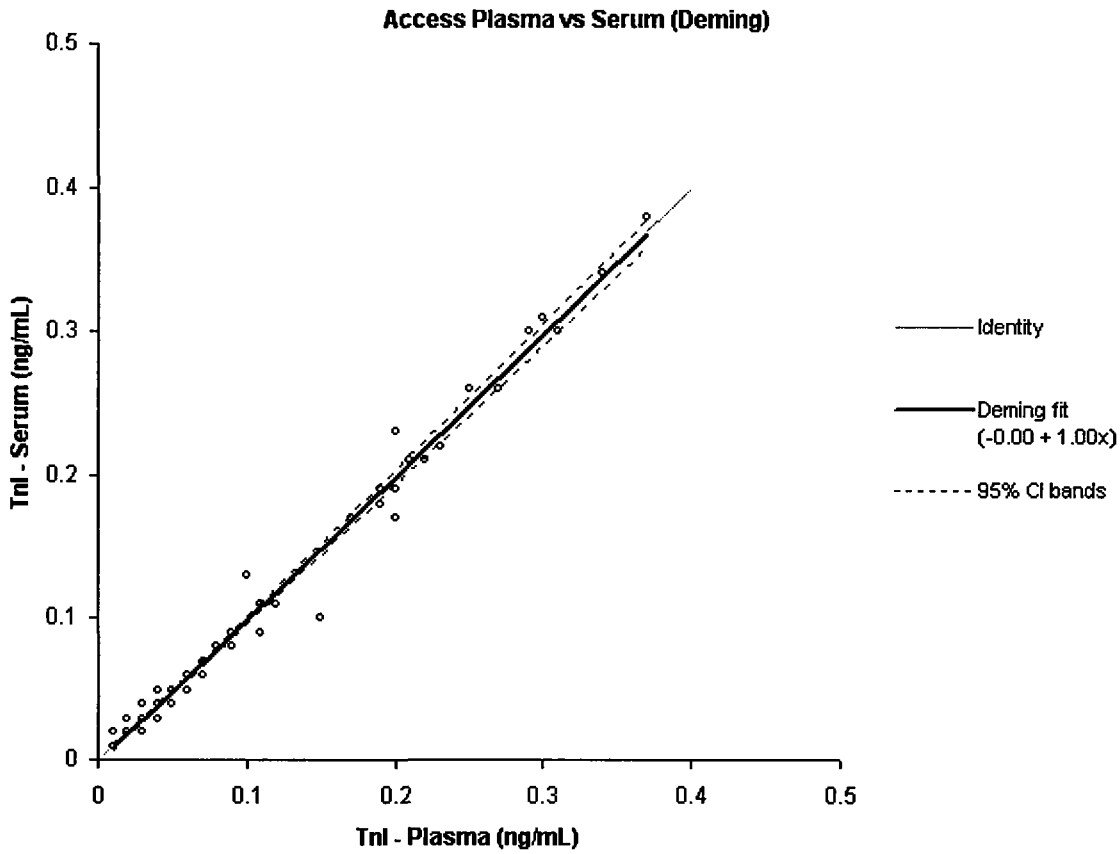
To address Dr. Elder's instruction that we focus on specimens from patients with TnI concentrations near the clinical cut off, BEC has performed a Deming regression analysis of results from paired serum and plasma samples with troponin levels from 0.01 to 0.4 ng/ml. Similar to what was observed in the wider range analysis, excellent agreement between the two matrices was observed. N = 86, slope = 1.00, Y-intercept = 0.00, r = 0.99. See Figure 4-1 below:

Figure 4-1: Deming Regression of Plasma vs. Serum



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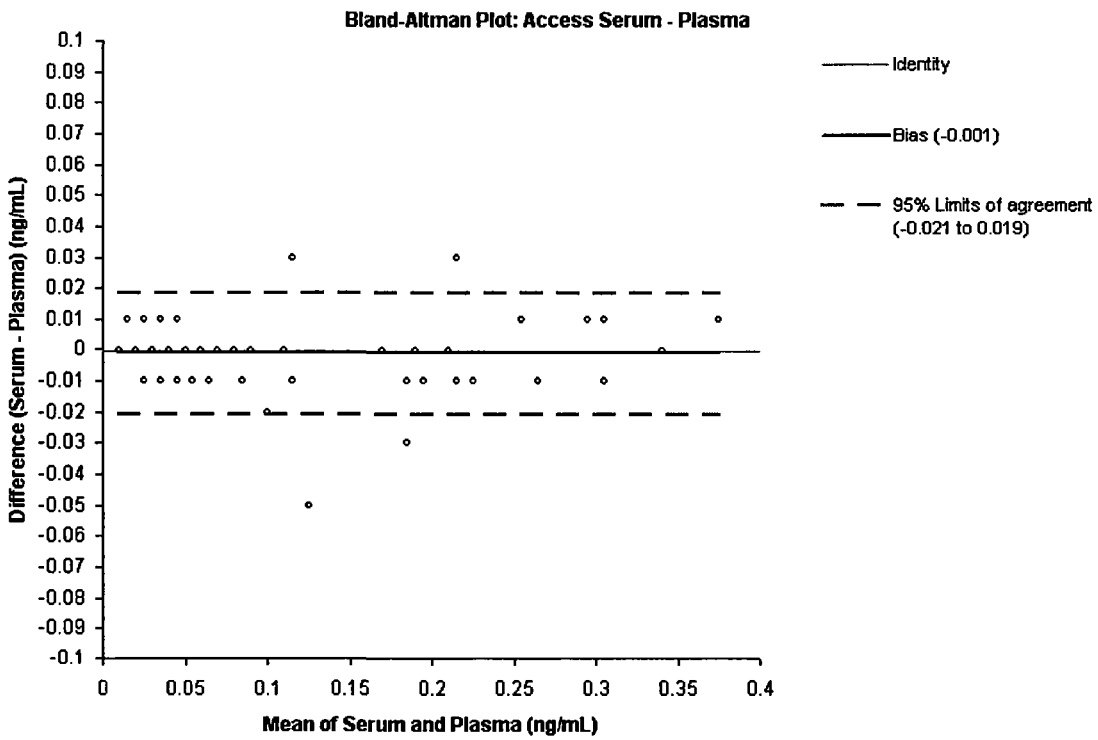
BEC has also performed additional statistical analyses of the data from the clinical sample matrix comparison study to demonstrate that the assay will reliably predict the clinical performance of both sample types at the established diagnostic cutoffs.

For example, we performed a Bland-Altman analysis of bias for the same specimens with values in the clinically-relevant range between 0.01 and 0.40 ng/ml. As the Bland-Altman plot below (Figure 4-2) shows, there was only a small degree of random distribution around a near-zero bias (-0.001), indicating no systemic bias between the two sample matrix types.

Figure 4-2: Bland-Altman Plot: Serum-Plasma



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Next, to investigate the clinical concordance between the two sample types around the 0.03 ng/ml recommended clinical cut-off, we performed McNemar's test on the serum and plasma data from all 123 subjects for which both specimen types had been tested. The table below (Table 4-1) shows excellent concordance with no significant differences (p = 0.65) between serum and lithium heparin plasma.

Table 4-1: McNemar Test for Plasma vs. Serum Concordance Analysis

Access AccuTnI: Plasma vs Serum Concordance Analysis
McNemar's Test: p=0.65
96% agreement between plasma and serum (118/123)

	Serum <0.03	Serum ≥0.03	Total
Plasma <0.03	38 (30.9%)	3 (2.4%)	41 (33.3%)
Plasma ≥0.03	2 (1.6%)	80 (65.0%)	82 (66.7%)
Total	40 (32.5%)	83 (67.5%)	123 (100%)

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Finally, to further examine the clinical utility of the matched serum and plasma specimens from the pivotal trial, we constructed Receiver Operating Characteristic curves (ROC) for each matrix using results from all 123 subjects with both serum and plasma data. As shown in Figure 4-3 and Table 4-2 below, the two specimen types showed equivalent diagnostic efficacy. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum, respectively.

Figure 4-3: Receiver Operating Characteristic Curves, Plasma vs. Serum

ROC Curves, Plasma vs. Serum
Study TnI - Access
Adjudicator Diagnosis

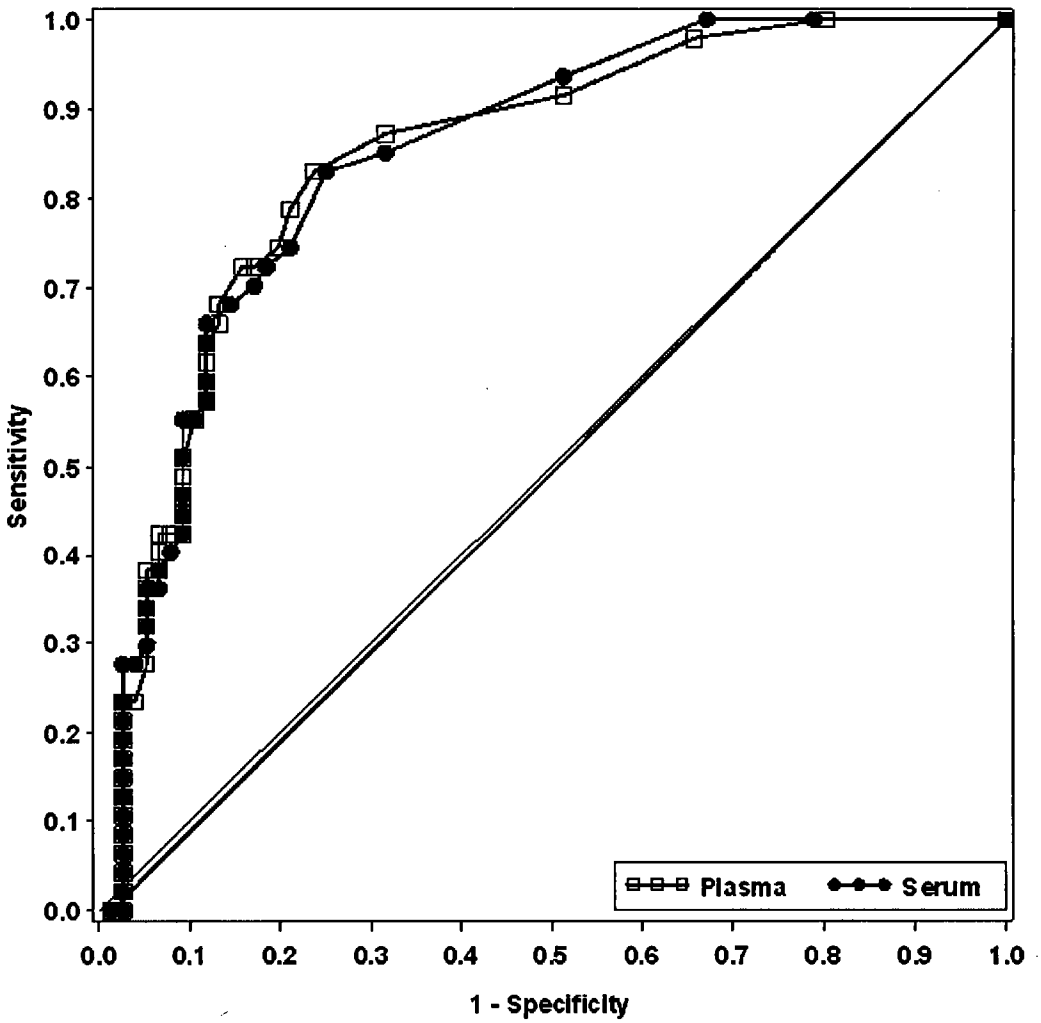

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Table 4-2: p-value for Comparison of AUCs, Serum vs. Plasma

N_{MI}	$N_{Non\text{-}MI}$	Matrix	AUC	95% Confidence Interval	p-value
47	76	Plasma	0.845	0.775 - 0.916	0.876
.	.	Serum	0.847	0.778 - 0.915	
p-value for comparison of AUCs between serum vs. plasma samples					

Following the guidance we received from FDA in response to our inquiry regarding method comparison, BEC has demonstrated a high degree of agreement in correlation, concordance, lack of bias, and equivalent diagnostic efficacy between serum and lithium heparin plasma for specimens both near the clinical cut-off and at higher levels. Therefore, the data demonstrate the equivalence of the two sample matrices, without the need for additional clinical studies, and that the claim for both serum and lithium heparin plasma should be retained in our statement of intended use.

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Question 5: Limits of Detection

FDA: The limits of detection for the AccuTnI assay were assessed through a series of studies. However, most of these studies were not performed following the instructions in the package insert. Importantly, while you claim that the instrument calibration is stable for 56 days, many of these studies were performed by generating a calibration curve for each run or at each temperature tested. Therefore we have the following concerns with your studies.

5.a. *FDA: Limit of the blank (LoB): You performed a standardized LoB study and a multi temperature LoB study. However, a calibration curve was generated with each run for the standardized study and a calibration curve was generated with each run at each temperature for the multi temperature LoB study. Since both of these studies were not performed as the device is intended to be use[d], we cannot interpret your results. We do not believe that your study design supports the statement that the LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C. Please provide new LoB studies following the exact instructions in your package insert (particularly your calibration claim) to determine the LoB and to support your claim that the LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.*

BEC Response to Question 5.a.

The AccuTnI+3 LoB studies were performed according to a protocol based on CLSI EP17-A, "Protocols for Determination of Limits of Detection and Limits of Quantitation: Approved Guideline", to analytically determine the detection capability of the device. Per CLSI guideline EP17-A, in order to establish performance characteristics the manufacturer must include multiple variables. "... manufacturers shall consider performing the study on two or more instruments with two or more lots of reagents to attempt to capture the variability expected with different instrument/reagent systems." Therefore, BEC incorporated variables such as multiple reagent lots, multiple instruments, multiple days, multiple calibrations, and multiple temperatures into our study designs as described in our pre-IDE. The requirements of EP17-A preclude using a single calibration curve.

To demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18 °C to 28 °C, we reanalyzed all sample results from the multi-temperature LoB study data using calibration curves generated at 18 °C and 28 °C. Because we were able to reanalyze the existing LoB data, it was not necessary to repeat these studies. Refer to our response to Question 1.b. for a description on how this analysis was performed. Table 5-1 below shows sample results from the multi-temperature LoB study when measured using calibrations performed at 18 °C, 28 °C, and as originally submitted (All Temperatures Combined).

Table 5-1: LoB by Calibration Temperature

	Calibration Temperature		
Statistic	**18 °C**	**All Temperatures Combined***	**28 °C**
Measured LoB (ng/mL)	0.002	0.002	0.002
Upper Bound LoB (ng/mL)	0.003	0.003	0.003

* "All Temperatures Combined" is the multi-temperature data originally included in the Submission and is provided for comparison purposes.

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Conclusion: There is little to no impact of calibration temperature on the derived values for LoB. Regardless of the temperature at which the system was calibrated, our estimate of LoB meets acceptance criteria of LoB ≤ 0.010 ng/mL at each ambient temperature tested between 18 °C and 28 °C. Therefore, LoB is not affected by changes in ambient temperature across the operating range of 18 °C to 28 °C.

5.b. *FDA: Limit of detection (LoD): You performed 2 studies to determine the LoD of your assay. The standardized study was comprised of 12 runs on 3 instruments with 2 reagent lots and 2 calibrator lots per instrument at each of 3 ambient temperatures. A calibration curve was generated with each run. For the multi-temperature study, 5 lithium heparin plasma samples were tested in replicates of 3 for each of 12 runs on 3 instruments, 2 reagent lots and 2 calibrator lots at 18°C, 20°C, 22°C, 24°C, 26°C and 28°C (± 2°C for each temperature setting). A calibration curve was generated with each run at each temperature. Since neither of these studies was performed as this device is intended to be used, we do not know how to interpret your results (please see 1b for additional discussion regarding our concern with your calibration approach). Currently, your study design does not support the statement that the LoD is not affected by changes in ambient temperature across the operating range of 18C to 28C. You should repeat the LoD studies following the instructions in your package insert (particularly your calibration claim). Please also closely follow the recommendation in CLSI EP17 and provide the exact formula(s) used to determine the LoD.*

BEC Response to Question 5.b.

The calibration discussion provided in our response to Question 1.b. and the study design discussion in our response to Question 5.a. directly apply to LoD as well. Regardless of the temperature at which calibration is performed, LoD results obtained at any temperature within the ambient temperature operating range (18 °C - 28 °C) are acceptable.

To demonstrate that the LoD is not affected by changes in ambient temperature of calibration across ambient operating temperature range of 18 °C to 28 °C, we reanalyzed the multi-temperature LoD study data using calibration curves generated at 18 °C and 28 °C following the EP17-A guideline. Because we were able to reanalyze the existing LoD data, it was not necessary to repeat these studies. Refer to our response to Question 1.b. for a description on how this analysis was performed.

Table 5-2 below displays sample results from the multi-temperature LoD study as measured using calibrations performed at 18 °C, 28 °C, and as originally submitted (All Temperatures Combined). The additional analysis summarized in Table 5-2 represents the worst case scenario because multiple calibration curves generated at different temperatures from the sample testing on different days were used to recalculate the sample results. This method of analysis produces very conservative estimates of LoD.

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Table 5-2: LoD by Calibration Temperature

Statistic	Calibration Temperature		
	18 °C	All Temperatures Combined*	28 °C
Measured LoD (ng/mL)	0.007	0.008	0.008
Upper Bound LoD (ng/mL)	0.008	0.009	0.010

* "All Temperatures Combined" is the multi-temperature data originally included in the Submission and is provided for comparison purposes.

Conclusion: There is little to no impact of calibration temperature on the calculated values for LoD. Regardless of the day and the temperature at which the assay was calibrated, LoD results meet acceptance criteria of LoD ≤ 0.030 ng/mL at each ambient temperature tested between 18 °C and 28 °C. Therefore, LoD is not affected by changes in ambient temperature across the operating range of 18 °C to 28 °C.

As requested, the exact formulas used to determine LoD are provided below:

LoD is calculated as follows.

The combined standard deviation (SDs) is computed by combining the within-run standard deviations obtained for the samples:

$$SDs = sqrt((SD_{S1}^2 + SD_{S2}^2 + SD_{S3}^2 + SD_{S4}^2 + SD_{S5}^2)/5)$$

From EP17, the constant is determined as follows (NS = Total Replicates, K = # of samples):

$$Constant = 1.645/(1 - [1 / (4 \times (NS - K)])$$

The measured LoD is then calculated as follows:

$$LoD = LoB + Constant \times SDs$$

An "upper bound" LoD is then calculated using either the 97.5th percentile estimate of the LoB or the highest observed within-run standard deviations from individual LoD samples.

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5.c. *FDA: Limit of quantitation (LoQ): You performed 2 different experiments to determine the LoQ of your device. The standardized LoQ study was performed using 7 lithium heparin plasma samples with low levels of troponin. Each sample was tested in replicates of 3 for each run. The study was performed on 3 instruments using 3 reagent lots at 18°C, 28°C and NLC (defined as normal laboratory conditions ranging from 21°C to 25°C). A single calibration curve was generated at each temperature. For the multi temperature study, 7 samples were prepared and each sample was tested in replicates of 3 for each run. A total of 24 runs were completed using 3 instruments, 2 reagent lots and 2 calibrator lots. A single calibration curve was generated at 24°C for this study. Because of the different calibration approaches, your experiments were difficult to interpret (see 1b). From the precision profile you determined the concentrations corresponding to a 10% and 20% total CV by interpolation. We do not concur with determining the LoQ based on interpolation of your data. According to our review of your data, from the standardized LoQ study, at 18C the lowest value was a CV less than 10% is 0.026 ng/mL, at NLC it is 0.030 ng/mL and at 28C it is 0.044 ng/mL. Therefore, according to this data, your LoQ is 0.044 at 10% CV (0.29 ng/mL for a CV less than 20%). Meanwhile, for the multi-temperature LoQ precision results the lowest value with a CV less than 20% and 10% is 0.027. Therefore, your studies do not support your claim that the LoQ is 0.03 ng/mL at 10% CV and 0.01 ng/mL at 20% CV. Furthermore, we are very concerned that your LoQ seems to differ depending on the temperature (i.e. 0.044 ng/mL at 28°C, 0.030 ng/mL at NLC and 0.026 ng/mL at 18°C). We have serious concerns that you have not resolved the thermal sensitivity issue since the LoQ of your device seems to depend on the ambient temperature (please refer to item 1). Once you have resolved your temperature sensitivity issue, please provide new LoQ studies following the exact instructions in your package insert (particularly your calibration claim) to determine the LoQ for your device and to support your claim that the LoQ is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.*

BEC Response to Question 5.c.

At FDA's request, BEC reanalyzed the originally-submitted LoQ data using the guidance of EP17-A. For each temperature (18 °C, NLC and 28 °C), a set of twenty-one studies were conducted including fourteen samples, three reagent lots and six Access 2 instruments. Each LoQ study included over 60 replicates over multiple days meeting the EP17-A requirement for an LoQ study of at least 40 replicates. At each temperature, the results from multiple reagent lots and instruments were pooled together in order to have a robust estimate of the imprecision. Table 5-3 below contains a summary of the LoQ results:

Table 5-3: LoQ Summary Table

	Temperature Condition		
	18 °C	**NLC**	**28 °C**
10% LoQ	0.022 ng/mL	0.026 ng/mL	0.029 ng/mL
20% LoQ	0.011 ng/mL	0.011 ng/mL	0.024 ng/mL

The following tables (Table 5-4, Table 5-5, and Table 5-6) list the results of each set of temperature studies sorted by mean sample troponin concentration. In each table, the grey highlighted data point is the lowest concentration sample that achieved 20% CV; the yellow highlighted data point is the lowest concentration sample that achieved 10% CV.

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Table 5-4: LoQ Results at 18 °C

Sample	Lot	Instrument	Mean ng/mL	%CV
A1	116676	501007	0.009	21
A1	116678	402358	0.011	13
A1	116677	502884	0.012	11
A2	116676	501007	0.022	8
A2	116677	502884	0.022	10
A2	116678	402358	0.026	9
A3	116676	501007	0.031	5
A3	116677	502884	0.031	7
A3	116678	402358	0.034	8
A4	116676	501007	0.051	5
A4	116677	502884	0.051	4
A4	116678	402358	0.056	4
A5	116676	501007	0.084	3
A5	116677	502884	0.084	4
A5	116678	402358	0.095	5
A6	116677	502884	0.140	4
A6	116676	501007	0.145	2
A6	116678	402358	0.158	5
A7	116677	502884	0.223	4
A7	116676	501007	0.226	3
A7	116678	402358	0.251	3

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Table 5-5: LoQ Results at NLC

Sample	Lot	Instrument	Mean ng/mL	%CV
B1	116678	501022	0.008	22
B1	116677	507310	0.011	19
B1	116676	500616	0.012	19
B2	116678	501022	0.016	17
B2	116677	507310	0.020	14
B2	116676	500616	0.022	13
B3	116678	501022	0.026	7
B3	116677	507310	0.027	7
B3	116676	500616	0.030	8
B4	116678	501022	0.048	4
B4	116677	507310	0.049	6
B4	116676	500616	0.054	5
B5	116678	501022	0.080	3
B5	116677	507310	0.081	5
B5	116676	500616	0.089	4
B6	116678	501022	0.139	2
B6	116677	507310	0.141	5
B6	116676	500616	0.148	3
B7	116678	501022	0.271	3
B7	116677	507310	0.273	5
B7	116676	500616	0.289	4

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Table 5-6: LoQ Results at 28 °C

Sample	Lot	Instrument	Mean ng/mL	%CV
B1	116678	501007	0.008	29
B1	116676	502884	0.010	21
B1	116677	402358	0.013	38
B2	116678	501007	0.014	25
B2	116676	502884	0.019	21
B2	116677	402358	0.024	20
B3	116678	501007	0.026	14
B3	116676	502884	0.029	5
B3	116677	402358	0.033	8
B4	116678	501007	0.044	5
B4	116676	502884	0.047	5
B4	116677	402358	0.050	5
B5	116678	501007	0.064	4
B5	116676	502884	0.075	5
B5	116677	402358	0.076	9
B6	116678	501007	0.121	4
B6	116676	502884	0.131	3
B6	116677	402358	0.145	8
B7	116678	501007	0.233	4
B7	116676	502884	0.256	4
B7	116677	402358	0.275	8

Conclusion: These results meet the pre-established acceptance criteria of LoQ < 0.06 ng/mL. The lowest concentration sample with less than or equal to the expected imprecision determines the LoQ. The AccuTnI+3 10% LoQ will be reported as 0.03 ng/mL and the 20% LoQ will be reported as 0.02 ng/mL. BEC has updated the product IFU to reflect the new analysis. See Appendix 9.

These results are different from the Agency's results of 10% LoQ of "0.044 ng/mL at 28 °C, 0.030 ng/mL at NLC and 0.026 ng/mL at 18°C" because of how the data are pooled. Consistent with EP17-A, to derive a robust estimate around 10% and 20% CV, BEC pooled data from all three instruments (21 samples) at a given temperature, whereas the Agency evaluated each dataset on each instrument (7 samples) individually. Analyzing the sample distribution of each individual sample set (n = 7 on each instrument) is not sufficient to establish an accurate estimate of LoQ.

When data from all three instruments at a given temperature are combined, however, there are enough data points near the 10% and 20% LoQ values in order to conduct a robust analysis. FDA's estimate of LoQ at 0.044 ng/mL is based on the single instrument 501007 result at 28°C, and on a limited number of samples. The sample at 0.044 ng/mL had a total CV result of 5%, which is well below the 10% LoQ threshold. Use of this sample alone does not provide the best estimate of the 10% LoQ of the AccuTnI+3 assay. Furthermore, the results for sample Pr 1 included in the new multi-temperature EP5-A2, "Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline-Second Edition"

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precision study described in our response to Question 10, demonstrates that the total imprecision at a TnI concentration of 0.04 ng/mL is consistently below 10% total CV.

FDA expressed "serious concerns" that the LoQ of the AccuTnI+3 device seems to depend on the ambient temperature.

- ◊ Using EP17-A, the estimated LoQ is entirely dependent upon the concentration of the samples used in the studies rather than the temperature at which they were conducted.
- ◊ One sample set was used for studies conducted at 18 °C, and a second sample set was used for studies conducted at NLC and 28 °C. In addition, these studies used different instruments and calibrations. Therefore, direct comparisons among the individual studies are not possible.
- ◊ No differences were seen between the calculated results for LoQ at NLC and 28°C, which used the same samples. No bias is seen between the sample concentrations at either temperature or the LoQ results derived per EP17-A. As such, the results are entirely distinct from the original Concordance Study which showed an apparent thermal bias.
- ◊ The pre-established acceptance criteria for LoQ studies were that 10% total imprecision would be achieved at a concentration less than 0.06 ng/mL and 20% total imprecision would be achieved at a concentration less than 0.03 ng/mL.
- ◊ LoQ results achieved this objective for each temperature condition, and the broadest range results (0.029 ng/mL rounded to 0.03 ng/mL at 28 °C for 10% CV and 0.024 ng/mL rounded to 0.02 ng/mL at 28 °C for 20% CV) are used as the claimed LoQ.

The 10% LoQ at 0.03 ng/mL and the 20% LoQ at 0.02 ng/mL were established using multiple instruments, multiple reagent lots, multiple calibrations, and multiple temperatures for the operating temperature range of the assay. Small differences noted in LoQ, therefore, cannot be solely attributed to thermal sensitivity of the assay.

Additional Analysis:

The impact of calibration temperature on the calculated LoQ results was also assessed. All sample results in the original multi-temperature LoQ study were reanalyzed from calibrations performed at 18 °C, NLC, and 28 °C. LoQ was calculated per EP17-A for each calibration scenario; Table 5-7 below displays the results. These data indicates that there is little to no impact of calibration temperature on the derived values for LoQ. Because we were able to reanalyze the existing LoQ data, it was not necessary to repeat these studies. Refer to our response to Question 1.b. for a description on how this analysis was performed.

Table 5-7: LoQ by Calibration Temperature

	Calibration Temperature		
Statistic	**18 °C**	**24 °C**	**28 °C**
10% CV LoQ (ng/mL)	0.028	0.026	0.026
20% CV LoQ (ng/mL)	0.009	0.017	0.011

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5.d. FDA: Please clarify if the patient samples for the LoD and LoQ studies are spiked with exogenous troponin or if the patient samples are all natural, unmodified patient samples. We recommend that for your new LoD and LoQ studies, you should use natural, unmodified patient samples to determine your claims.

Additional FDA response from November 7, 2012: *We still recommend that you provide data for all requested studies using natural patient samples (i.e., not spiked with exogenous cTnI analyte). However, we agree that the use of pooled patient samples with relevant cTnI concentrations (that are not spiked with exogenous cTnI analyte) are acceptable for the requested studies (i.e., LoD, LoQ, field effectiveness studies and precision studies).*

BEC Response to Question 5.d.

Samples used in the studies to establish the LoD and LoQ for the device were natural patient sample pools and were not spiked with exogenous troponin.

5.e. FDA: Please also address the item listed in 1d (instrument temperature set points).

BEC Response to Question 5.e.

Please see BEC's response to Question 1.d.

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Question 6: Linearity

FDA: You performed 12 standardized studies to evaluate the linearity of your device. Four studies were performed at 18 °C, 28 °C and NLC (21C to 25C) using 2 lots or reagents and 2 instruments. You used a synthetic matrix (buffered bovine serum albumin) for your samples. The results of your linearity studies are summarized in the following table:

Temp	Reagent	Instrument	Slope	Intercept
18°C	116677	501007	0.8755	0.0014
18°C	116677	502884	0.8467	0.0002
18°C	116678	501007	0.8593	0.0000
18°C	116678	502884	0.8263	0.0000
NLC	116677	500616	0.9513	0.0005
NLC	116677	507310	0.9137	0.0008
NLC	116678	500616	0.9367	0.0003
NLC	116678	507310	0.9103	0.0007
28°C	116677	501007	1.127	0.0010
28°C	116677	502884	1.053	0.0004
28°C	116678	501007	1.122	0.0014
28°C	116678	502884	1.043	0.0003

Your acceptance criteria are that the higher order (2nd and 3rd) term of the polynomial fit must be non-significant. If it is significant, the fit of the polynomial regression demonstrating significance must have a bias at each sample tested of ≤ 16% for doses > 0.105 ng/mL or ≤ 0.0168 ng/mL for doses ≤ 0.105 ng/mL. Based on these results, you concluded that "all reagent pack lot and instrument combinations met the acceptance criteria for linearity at the 3 ambient temperature conditions tested and demonstrates linearity across the measuring range." We do not concur with your conclusion. Specifically:

6.a. *FDA: Based on your data, the linearity varies depending on the temperature. Specifically: 18°C, the slope of your experiments range from 0.8263 to 0.8755, at NLC, the slopes range from 0.9103 to 0.9513 and at 28°C, the slopes range from 1.053 to 1.127 demonstrating differences in the performance of this assay depending on the temperature. We have serious concerns that you have not resolved the thermal sensitivity issue and the test results obtained using your device can differ depending on the ambient temperature (please refer to item 1).*

BEC Response to Question 6.a.

The temperature dependence of the slopes calculated by FDA from the data provided in the linearity studies was caused by the non-native composition of the sample. The original linearity studies used the same antigen as the AccuTnI+3 calibrator, a recombinant troponin I protein which was diluted in synthetic matrix. As described in Appendix 2, unlike native troponin analyte, the calibrator is not thermally sensitive. Therefore, the application of the thermal algorithm to the calibrator results was unnecessary, and caused the temperature dependence of the first order linear regression slopes that compared expected to observed results. Accordingly, BEC has repeated the linearity study using the appropriate native cardiac troponin I analyte and native matrix. See our response to Question 6.c.

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6.b. *FDA: Furthermore, as we discussed under pre-IDE I100255/S002, we are concerned that your acceptance criteria are too broad for the intent of this testing. Once you resolve the temperature sensitivity issue, please perform new linearity studies. We recommend that you tighten your acceptance criteria based on the medical needs of your proposed device.*

BEC Response to Question 6.b.

See our general discussion of acceptance criteria in our response to Question 1.b.

The acceptance criteria for deviation from linearity was based on two times the device imprecision (2 x 8% = 16% for high samples or 0.0084 x 2 = 0.0168 ng/mL for low samples). This specification is applied to the *individual* samples in each study and is not an overall estimate of deviation from linearity.

- ◊ Using the EP6-A "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach: Approved Guideline," the concentrations above LoD where percent difference from linearity is measurable are well above the medical decision point (URL) of the assay.
- ◊ Using the 8% expected total imprecision of the assay and assuming this is composed of 6% within- run and 5% between-run imprecision [sqrt(6%^2 + 5%^2) ~ 8%] then the 4 replicates measured at each concentration would give a standard error of the mean estimate of sqrt(6%^2/4 + 5%^2) = 5.83%.
- ◊ The difference between two such estimates (e.g., linear vs. quadratic points) would have a 95% confidence interval of 5.83% * sqrt(2) *1.96 , which is approximately 16%
- ◊ Therefore, with 108 assumed random comparisons (12 studies of 9 sample concentrations each) the probability of seeing no comparisons beyond this criteria is 0.95^108 = 0.004. Since no such failing comparisons were seen then we are 99.6% certain that the linearity results are within the expected variability of the assay.

6.c. *FDA: Since we do not know if a synthetic matrix will mimic the performance of your device on patient samples, we recommend that you perform the studies using intended use patient samples (e.g. lithium heparin patient samples).*

BEC Response to Question 6.c.

As the Agency requested, BEC has repeated the linearity study in total, using native cardiac troponin I analyte and native matrix (lithium heparin plasma). The linearity study was performed to satisfy the recommendations of EP6-A with samples spanning the entire assay dynamic range. Four independent studies were performed on two reagent lots and two instruments at each of three temperature conditions including 18 °C, NLC, and 28 °C. Performance was assessed relative to the following acceptance criteria:

- ◊ The higher order (2nd or 3rd) term of the polynomial fit should be non-significant ($p>0.05$).
- ◊ If significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias ≤16% for doses >0.105 ng/mL or ≤0.0168 ng/mL for doses ≤0.105 ng/mL in comparison to the linear regression fit.

The results are summarized in Table 6-1, Table 6-2, and Table 6-3 below. All studies at all temperatures meet the predefined acceptance criteria for linearity. Linearity results, including higher order fitted estimates, linearity plots, and difference tables are provided in Appendix 6.

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Table 6-1: Summary of Linearity Results at 18 °C

		18 °C Testing		
Instrument #	Reagent Lot	p-value <0.05?	Maximum Deviation from Linearity	Pass/Fail
500006	225961	Yes	-14%	Pass
504050	225961	Yes	-12%	Pass
500006	225962	Yes	-11%	Pass
504050	225962	Yes	9%	Pass

Table 6-2: Summary of Linearity Results at NLC

		NLC Testing		
Instrument #	Reagent Lot	p-value <0.05?	Maximum Deviation from Linearity	Pass/Fail
500006	225961	Yes	-11%	Pass
504050	225961	Yes	9%	Pass
500006	225962	Yes	-12%	Pass
504050	225962	Yes	-14%	Pass

Table 6-3:Summary of Linearity Results at 28 °C

		28 °C Testing		
Instrument #	Reagent Lot	p-value <0.05?	Maximum Deviation from Linearity	Pass/Fail
500006	225961	Yes	7%	Pass
504050	225961	Yes	7%	Pass
500006	225962	Yes	-8%	Pass
504050	225962	Yes	4%	Pass

Using the updated data, BEC has reproduced a table similar to the one provided by the Agency to describe FDA's primary concerns over the original linearity results. As seen in Table 6-4 below, the linear slope comparing observed and expected results does not show temperature dependence.

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Table 6-4: Comparison of Slopes (Bias)

Temp	Reagent	Instrument	Slope	Intercept
18°C	225961	500006	0.941	0.001
18°C	225961	504050	0.950	0.000
18°C	225962	500006	0.956	0.000
18°C	225962	504050	0.968	0.000
NLC	225961	500006	0.961	0.000
NLC	225961	504050	0.964	0.000
NLC	225962	500006	0.963	0.000
NLC	225962	504050	0.950	0.001
28°C	225961	500006	0.967	0.001
28°C	225961	504050	0.975	0.001
28°C	225962	500006	0.960	0.000
28°C	225962	504050	0.983	0.000

Conclusion: All reagent pack lot and instrument combinations met the acceptance criteria for linearity at the three ambient temperature conditions tested, showing linearity across the measuring range. The AccuTnI+3 assay on Access 2 thus demonstrates linearity, independent of the ambient temperature.

When using native troponin antigen and matrix, the temperature dependence of the linear slopes noted by the Agency in the original Linearity Study is not reproduced. Thus, the results of the original Linearity Study do not represent a failure of the thermal algorithm to appropriately adjust patient sample results across the operating temperature range.

6.d. FDA: Please also address the item listed in 1d (instrument temperature set points).

BEC Response to Question 6.d.

Please see BEC's response to Question 1.d.

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Question 7: Field Effectiveness Study

FDA: You performed internal and external "Field Effectiveness" studies to assess the precision of the AccuTnI assay when used with the thermal algorithm on the Access 2 instruments. We have the following concerns with your studies:

7.a. *FDA: For the internal study, you used 5 cTnI commercial controls. The ambient temperature of the lab cycled (from 18C to 28C) to reflect the worst case thermal profile for Access AccuTnI customers. The acceptance criterion is defined as the variance of the thermal-algorithm-adjusted results for each sample on each instrument must be less than or equal to the unadjusted results. Precision of the thermal algorithm adjusted results for the samples on each instrument must be ≤ 8% CV for concentration > 0.105 ng/mL and ≤0.0084 ng/mL standard deviation for concentrations ≤ 0.105 ng/mL.*

7.a.i. *FDA: We are concerned that your acceptance criteria for normal troponin values and values around the medical decision point may be too broad. We recommend that you tighten these criteria based on the medical needs of this assay and also include acceptance criteria for temperature bias.*

Internal vs. External Field Effectiveness Studies

The internal study was designed to evaluate the precision of the Access AccuTnI+3 on the Access 2 Immunoassay Systems under a controlled range of temperature conditions that may occur from time to time in the field.

The external study design, in contrast, evaluated the precision of all three AccuTnI+3 reagent lots in multiple laboratories over multiple days/runs, in the hands of clinical laboratory technologists. Because the external laboratories were also performing their routine diagnostic testing with other instruments located in the lab, it would have been impractical or inappropriate to require the labs to undergo wide swings in ambient temperature. However, study staff at the participating labs monitored and documented the lab ambient temperatures, as described in the sections below.

BEC Response to Question 7.a.i.

See our general discussion of acceptance criteria in our response to Question 1.b.

The acceptance criteria for overall precision for AccuTnI+3 are consistent with the MI guidelines[2]: CV ≤8% for TnI concentrations > 0.105 ng/mL; SD ≤ 0.0084 for TnI concentrations ≤ 0.105 ng/mL

- ◊ If a positive TnI result is obtained, serial measurements are recommended, in order to detect a clinically significant 20-30% rise and/or fall of TnI concentrations[6].
- ◊ To detect a TnI concentration change of 20-30% with 95% probability, the device total imprecision (%CV) must be between 5% and 10%[6,7]. Therefore, a device with a total imprecision claim of 8% is capable of detecting clinically significant changes in TnI levels.
- ◊ Using an accepted medical decision point of 0.06 ng/mL (dose at 10% CV for the current AccuTnI device), 1 standard deviation (SD) is equal to 0.006 ng/mL. BEC calculated the 95th percentile confidence limit, which is 0.0084 ng/mL.
- ◊ Based on the clinical use of the assay as an aid in the diagnosis of myocardial infarction, BEC believes that the specifications are appropriate for the intended use of the device, are substantially equivalent to other TnI devices, and therefore meet the medical needs of the assay.

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Additional Analysis:

BEC has performed additional analyses of temperature bias for the samples that were tested in the internal field effectiveness study. These follow-up analyses were similar to those described in our response to Question 1.b. The analyses are summarized in Table 7-1 below. The data show that the thermal bias observed for each instrument, following application of the thermal algorithm, is less than a 1% change in reported TnI concentration for every 1 °C change in ambient temperature. A change of less than 1% per degree Celsius translates to less than a 10% change over the entire18 °C – 28 °C temperature range. See our response to Question 1.c. for more discussion of the "1% per degree C" criteria.

Table 7-1: Thermal Bias Before and After Application of the Thermal Algorithm

	Before Algorithm		After Algorithm	
Instrument	**Change per °C**	**% Difference 28 °C vs. 18 °C**	**Change per °C**	**% Difference 28 °C vs. 18 °C**
500537	-3.25	-32.5	0.95	9.5
504050	-3.73	-37.3	0.57	5.7
507295	-3.16	-31.6	0.71	7.1

7.a.ii. FDA: We also recommend that you include several natural patient samples in your field effectiveness studies.

BEC Response to Question 7.a.ii.

The Field Effectiveness studies were requested by the Agency, and were specifically designed to provide additional confidence that the final AccuTnI+3 product in its entirety—including thermal algorithm, system software, assay protocol files, etc.—performs properly on fielded instruments. The study design challenged the thermal algorithm under conditions of broader variability than are typically encountered in the clinical laboratory environment, including:

- ◊ Multiple instruments of varying vintage
- ◊ Multiple ambient temperatures, constant and dynamic
- ◊ Multiple reagent lots
- ◊ Multiple test request scenarios including STAT, panels, reflex, etc.
- ◊ Multiple test scenarios under random access conditions including other assays

While natural patient samples or patient sample pools were evaluated wherever feasible, e.g., methods comparison, thermal sensitivity, and multi-temperature precision studies, the Internal Field Effectiveness Study for AccuTnI+3 on the Access 2 Immunoassay Systems could not use natural samples. Because it was an evaluation of imprecision in the presence of additional variability from several sources expected in the field, it required a significant volume of sample in order to complete numerous measurements of the same sample over time.

In this particular study, the volume required for each individual sample was in excess of 50 mL. This large

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volume precluded the use of individual, natural patient samples containing cardiac troponin, since individual, natural patient samples are typically available only in residual quantities of 1-2 mL each.

Samples used in the Internal Field Effectiveness Study were commercial quality controls ("QC") that reflect the thermal behavior of natural patient samples and yield results that are predictive of patient sample results. We used commercial QC in the Field Effectiveness Study because our customers would typically use these controls to assess the assay's performance and to detect any performance issues before testing patient specimens. By using commercial QC in our Internal Field Effectiveness Study, we evaluated the performance of the device as our customers would and as it is intended to be used in the field.

7.b. FDA: For the external study, you used 5 external sites that performed a multi-day precision study on Access 2 instruments using tri-level commercial quality control samples from 2 sources. Your acceptance criteria is that the variance of the adjusted results for each sample greater than the 10% CV LoQ acceptance criteria of 0.06 ng/mL must be less than or equal to the unadjusted results. Precision of the thermal algorithm adjusted results for the samples on each instrument must be ≤ 8% CV for concentration > 0.105 ng/mL and ≤ 0.0084 ng/mL standard deviation for concentrations ≤ 0.105 ng/mL.

7.b.i. FDA: It seems that you did not monitor the temperature changes (if any) that occurred during this testing. In order for this field testing to demonstrate that the solution to your thermal sensitivity issue is valid, you should make sure that temperature changes (encompassing your ambient temperature claim) occur during the course of the study and that those temperature changes are documented.

BEC Response to Question 7.b.i.

Laboratory ambient temperatures (in °C) were consistently monitored and documented throughout the field evaluation testing period at four of the five sites. Study site personnel were trained to record maximum and minimum temperatures in the testing labs each day that study testing was performed. While Site 5 correctly documented minimum daily lab temperatures, they did not always record maximum daily lab temperatures. Upon discovery of this deviation, the site was retrained to correctly perform lab temperature monitoring. Based on the lab temperature patterns observed at Site 5 during the Field Effectiveness Study and pivotal study testing, we concluded that the lab consistently operated within a temperature range of 18 °C and 20 °C during External Field Effectiveness Study testing and that all sample test data could be included in the analysis.

A summary of the laboratory temperatures measured during the External Field Effectiveness study is shown in Table 7-2 below. Because the study sites were also conducting their routine "production" testing on other instruments, they were not asked to purposely alter the laboratory temperature for this study. The ambient temperatures that were observed and documented were those that occurred without intervention during the course of normal activity and instrument operation in the laboratories. It is important to note that across these five sites, nearly the full range of acceptable ambient operating temperatures was observed.

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Table 7-2: Temperature Variations at External Field Effectiveness Study Sites

Testing Site	Mean Daily Temp Change	Min Daily Temp Change	Max Daily Temp Change	Min Temp (overall)	Max Temp (overall)
1	0.5 °C	0.2 °C	0.8 °C	22.0 °C	23.6 °C
2	1.7 °C	1 °C	3 °C	21 °C	24 °C
3	2.6 °C	1.7 °C	3.5 °C	23.9 °C	27.8 °C
4	1.6 °C	0.8 °C	3.6 °C	19.9 °C	24.5 °C
5	[redacted]	[redacted]	[redacted]	23.5 °C	25.2 °C

7.b.ii. FDA: We are also concerned that your acceptance criteria for normal troponin values and values around the medical decision point may be too broad. We recommend that you tighten these criteria based on the medical needs of this assay and also include acceptance criteria for temperature bias.

BEC Response to Question 7.b.ii.

See our general discussion of acceptance criteria in our response to Question 1.b.

The acceptance criteria for overall precision for AccuTnI+3 are consistent with the MI guidelines[2]: CV ≤8% for TnI concentrations > 0.105 ng/mL; SD ≤0.0084 for TnI concentrations ≤ 0.105 ng/mL

- ◊ If a positive TnI result is obtained, serial measurements are recommended, in order to detect a clinically significant 20-30% rise and/or fall of TnI concentrations[6].
- ◊ To detect a TnI concentration change of 20-30% with 95% probability, the device total imprecision (%CV) must be between 5% and 10%[6,7]. Therefore, a device with a total imprecision claim of 8% is capable of detecting clinically significant changes in TnI levels.
- ◊ The 0.0084 SD specification for low samples was derived from the expected variability (95% CI) around the current device's 10% LoQ at 0.06 ng/mL.
- ◊ Based on the clinical use of the assay as an aid in the diagnosis of myocardial infarction, BEC believes that the specifications are appropriate for the intended use of the device, are substantially equivalent to other TnI devices, and meet the medical needs of this assay.

7.b.iii. FDA: We also recommend that you include several unmodified natural patient samples in your field effectiveness studies.

BEC Response to Question 7.b.iii.

Precision studies require a significant volume of sample in order to complete numerous measurements of the same sample over time. For a more complete response, please refer to our response to Section 7.a.ii.above.

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Question 8: Interference

FDA: We have the following concerns with your study:

8.a. *FDA: You investigated potential interfering substances at 18°C, 28°C and NLC (21°C to 25°C) using 2 levels of interference added to lithium heparin plasma pools containing ≤0.01 ng/mL and 0.5 ng/mL troponin samples. Non-interference was defined for troponin values > 0.105 ng/mL as a percent change ≤ 10.0%. For normal samples, either the test sample must read less than or equal to the established 99th percentile URL (0.02); or, if the test samples exceed the established 99th percentile URL, the difference between the test and the control sample must be ≤ 0.01 ng/mL. We are concerned that since the lower concentration of troponin tested is below your LoQ, your results are difficult to interpret. Specifically, several individual replicates in the studies have higher troponin values than other replicates (which tend to have troponin values between 0 and 0.01 ng/mL). The following table lists the individual replicates:*

Compound	Temperature	Treatment Group	Replicate	Troponin result ng/mL
CTS Auto-gloss	NLC	CLS	10	0.0249
Triglyceride Intralipid	NLC	CLP	1	0.1633
Hemoglobin	NLC	TLP	7	0.0253
Trimethoprim	NLC	CLP	10	0.0260
Phenytoin	NLC	TLP	5	0.8676
	NLC	TLP	8	0.0436
Acetaminophen	NLC	CLS	7	0.0670
Simvastatin	28°C	TLS	9 and 10	0.035
Cinnarizine	28°C	CLS	7	0.028
Heparin-Sodium	28°C	CLP	4	0.051
Human serum albumin	28°C	CLP	4	0.023
	28°C	CLP	5 and 8	0.022

Furthermore, our review of your data indicates that phenytoin at 10 mg/dL at NLC significantly interfered with the performance of your assay since the mean of the treated group is 0.0915 (above the 99th percentile URL) and the untreated samples have a mean of 0. We recommend that you perform additional interference studies with allow troponin sample that is closer to the cut-off of your assay and above your LoQ in order to substantiate your interference claims.

BEC Response to Question 8.a.

The Agency stated that the negative/normal results are difficult to interpret and recommended an alternate testing concentration. Therefore, per the FDA recommendation, BEC conducted additional studies on all of the interferents at a TnI concentration close to the cutoff of the assay and above the LoQ of the assay. Since the original interference studies did not indicate any temperature impact on interference testing, the repeated testing was performed at normal laboratory conditions only. The following criterion was determined for this level of analyte prior to testing:

◊ The change must be ≤ 0.0084 ng/mL from diluent control for samples containing analyte at doses ≤ 0.105 ng/mL).

These results are presented in Table 8-1and Table 8-2 below, and all meet the acceptance criteria.

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Table 8-1: Additional interfering substance testing at ~0.05 ng/mL TnI

Substance Added	Concentration Added	Difference TnI Conc. ~0.05ng/mL
Acetaminophen	3 mg/dL	0.0003
	20 mg/dL	-0.0001
Acetylsalicylic Acid	50 mg/dL	0.0011
	65 mg/dL	-0.0007
Allopurinol	2 mg/dL	-0.0002
	40 mg/dL	0.0014
Ambroxol	8.6 mg/dL	-0.0004
	40 mg/dL	-0.0008
Ampicillin	1.8 mg/dL	-0.0003
	5 mg/dL	-0.0013
Ascorbic Acid	4 mg/dL	-0.0001
	6 mg/dL	-0.0018
Atenolol	0.2 mg/dL	-0.0008
	1 mg/dL	0.0002
Bilirubin (conj.)	5 mg/dL	-0.0005
	40 mg/dL	-0.0002
Bilirubin (unconj.)	4 mg/dL	-0.0026
	40 mg/dL	-0.0036
Biotin	10 ng/mL	0.0007
	290 ng/mL	0.0012
Caffeine	2 mg/dL	-0.0007
	10 mg/dL	0.0004
Captopril	0.5 mg/dL	-0.0009
	5 mg/dL	-0.0003
Cinnarizine	4.8 mg/dL	-0.0022
	40 mg/dL	-0.0014
Cocaine	1 mg/dL	0.0006
	2 mg/dL	-0.0006
CTS-Autogloss	1:1000 dilution	-0.0013
	1:100 dilution	-0.0012
Diclofenac	2 mg/dL	0.0008
	5 mg/dL	0.0010
Digoxin	2 ng/mL	0.0004
	200 ng/mL	-0.0005
Dopamine	30 mg/dL	0.0045
	65 mg/dL	0.0069
Erythromycin	2 mg/dL	-0.0007
	20 mg/dL	0.0015

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Table 8-2: Additional interfering substance testing at ~0.05 ng/mL TnI (cont.)

Substance Added	Concentration Added	Difference TnI Conc. ~0.05ng/mL
Fibrinogen	100 mg/dL	0.0011
	1000 mg/dL	-0.0029
Furosemide	3 mg/dL	-0.0011
	40 mg/dL	-0.0004
Hemoglobin	2 mg/mL	-0.0040
	5 mg/mL	-0.0048
Human Serum Albumin	5000 mg/dL	-0.0019
	6000 mg/dL	-0.0039
Ibuprofen	40 mg/dL	0.0008
	50 mg/dL	0.0006
Low MW Heparin	8 U/mL	-0.0003
	28.8 U/mL	0.0015
Methyldopa	0.75 mg/dL	-0.0011
	2.5 mg/dL	-0.0006
Nifedipine	20 ug/dL	0.0000
	60 ug/dL	-0.0019
Nitrofurantoin	0.2 mg/dL	-0.0009
	6.4 mg/dL	0.0019
Nystatin	0.7 mg/dL	-0.0011
	2.15 mg/dL	-0.0009
Oxytetracycline	0.5 mg/dL	-0.0008
	24 mg/dL	0.0019
Phenytoin	5 mg/dL	-0.0005
	10 mg/dL	-0.0001
Propranolol	1 ug/mL	-0.0012
	500 ug/mL	-0.0010
Quinidine	0.6 mg/dL	-0.0002
	2 mg/dL	-0.0001
Simvastatin	4 ug/mL	-0.0016
	200 ug/ml	0.0024
Theophylline	2 mg/dL	-0.0005
	25 mg/dl	-0.0017
Triglycerides	1000 mg/dL	-0.0011
	3000 mg/dL	0.0000
Trimethoprim	1.8 mg/dL	0.0000
	7.5 mg/dL	0.0002
Verapamil	0.1 mg/dL	-0.0012
	16 mg/dL	-0.0004
Warfarin	3 ug/mL	-0.0006
	30 ug/mL	0.0011

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8.b. FDA: We are also concerned that the acceptance criteria for the normal samples are too broad (according to our understanding, the allowable difference can be up to 50%). You should tighten your criteria when evaluating your new studies based on the medical needs of your assay.

BEC Response to Question 8.b.

See our general discussion of acceptance criteria in our response to Question 1.b.

The acceptance criteria for normal samples were developed based on the clinical utility of the assay as an aid in the diagnosis of AMI. As long as a sample is below the cutoff (0.02 ng/mL), it is considered to be within the normal range of the assay. Due to higher imprecision at very low TnI concentrations, we established our acceptance criteria for normal samples based on whether or not the interferent caused the result to cross the cutoff, rather than on a percentage change. It is not appropriate to use percentages to calculate dose shifts in this low concentration range, since a high percent shift would not indicate a high shift in dose (i.e., at a dose of 0.01 ng/mL, a 100% shift in dose would yield 0.02 ng/mL, which is still within the normal range). This is the same reason why BEC uses standard deviations instead of percent CVs at low doses.

However, since FDA indicated that the negative/normal results are difficult to interpret, BEC conducted additional studies on all of the interferents at a TnI concentration close to the cutoff of the assay and above the LoQ of the assay at ~0.05 ng/mL. Please refer to our response to Question 8.a. above.

8.c. FDA: Furthermore, we are concerned that your sodium heparin interference claim could be misinterpreted by the end users as an anticoagulant claim. Since interference studies are not sufficient to claim a specific anticoagulant, we recommend that you remove sodium heparin from your interference claim.

BEC Response to Question 8.c.

Sodium heparin was tested as a potential interferent since this substance was included in the original AccuTnI Instructions for Use. BEC recognizes that interfering substance testing alone is not sufficient to claim a specific anticoagulant. In order to avoid any potential confusion, this substance will be removed from the Analytical Specificity/Interferences claims section of the Instructions for Use.

8.d. FDA: We recommend that you test a higher concentration of triglycerides. Your predicate device tested 1000 mg/dL triglycerides while you tested 500 mg/dL. Please provide data evaluating at least 1000 mg/dL triglycerides on the performance of your device.

BEC Response to Question 8.d.

BEC has tested triglyceride at 1000 mg/dL (to be in alignment with the predicate device) and 3000 mg/dL (to be in compliance with EP7-A2's "Interference Testing in Clinical Chemistry; Approved Guideline-Second Addition" recommended upper level of reference interval). These data are summarized below in Table 8-3.

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Table 8-3: Triglyceride Testing at Higher Concentrations

Substance Added	Concentration Added	Observed (ng/mL) TnI Conc. 1			% Interference TnI Conc. 2		
		18 °C	NLC	28 °C	18 °C	NLC	28 °C
Triglycerides	1000 mg/dL	0.00	0.00	0.00	-1.6	-0.3	-0.3
	3000 mg/dL	0.00	0.00	0.00	-8.1	0.0	2.8

In addition, triglycerides were retested using a TnI sample at 0.05 ng/mL. This data is included in the additional interfering substance testing in Table 8-3 above and did not show any interference. In summary, these data show that triglycerides at these higher concentrations do not interfere in the AccuTnI+3 assay.

8.e. FDA: Please provide the rationale for the concentrations you tested for ambroxol, biotin, cinnarizine, cocaine, fibrinogen, Low MW heparin, nystatin, oxytetracycline, and simvastatin (i.e. are these therapeutic/endogenous or elevated or toxic?). Please see section 5.5 "Interferent Test Concentrations" in "Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition" for recommendations on appropriate test concentrations. If necessary, please provide data from testing at additional concentrations of these potential interfering compounds.

BEC Response to Question 8.e.

BEC developed the rationale for determining appropriate test concentrations for interfering substances using Section 5.5 of CLSI guideline EP7-A2, and information from the IFU of the predicate device:

Interferents were tested at two concentrations (low and high level).

Low level: BEC used a concentration of potential interferent within the reference interval (upper level) or within therapeutic concentration range (upper level), when evaluating drugs. This concentration was taken from:

- ◊ EP7-A2, when available
- ◊ The concentration stated in the predicate insert, if lower than the test concentration recommended in EP7-A2
- ◊ When different reference ranges were available, the highest dose specified was used.

High Level: BEC used the higher concentration of:

- ◊ The test concentration recommended in EP7-A2, when available
- ◊ The concentration used by the predicate insert

For substances not referenced in EP7-A2, nor in the predicate's package insert, the low concentration tested was the upper level of therapeutic concentration range seen in the blood; the high concentration tested was greater than three times the upper level of therapeutic range. These therapeutic ranges were determined primarily using the Physician's Desk Reference (PDR), or other sources as appropriate. The rationales for the concentrations for specific substances called out in the Letter (ambroxol, cinnarizine, cocaine, fibrinogen, low MW heparin, nystatin, oxytetracycline, and simvastatin) are outlined in Table 8-4, below.

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Table 8-4: Rationales for Interferent Concentration Selection

Interferent	Low Concentration	Low Concentration Rationale	High Concentration	High Concentration rationale
Ambroxol	8.6 mg/dL	Ambroxol low level concentration was calculated using 90 mg, the recommended daily dose, with 100% absolute bioavailability for an average 75 kg male (5.25L of blood).	40 mg/dL	Predicate Insert
Cinnarizine	4.8 mg/dL	Cinnarizine low level concentration was calculated using 50 mg, the upper level of the recommended dose range, with 100% absolute bioavailability for an average 75 kg male (5.25L of blood).	40 mg/dL	Predicate Insert
Cocaine	1 mg/dL	Predicate Insert	2 mg/dL	American Society of Health-System Pharmacists (AHFS) 5 times the upper level of therapeutic range
Fibrinogen	100 mg/dL	RxList[1] five times the upper level of reference interval	1000 mg/dL	Predicate Insert
Low MW Heparin[2]	0.5 mg/dL	PDR upper level single IV bolus of 30 mg.	7.1 mg/dL	PDR five times the upper level of therapeutic range
Nystatin	0.7 mg/dL	Predicate Insert	2.15 mg/dL	PDR five times the upper level of therapeutic range
Oxytetracycline	0.5 mg/dL	Predicate Insert	24 mg/dL	American Society of Health-System Pharmacists (AHFS) five times the upper level of therapeutic range
Simvastatin	0.4 mg/dL	PDR upper level of therapeutic range	2 mg/dL	PDR five times the upper level of therapeutic range

[1] Online database (www.rxlist.com). RiaSTAP was the drug used to determine fibrinogen interferent test concentrations.

[2] Low molecular weight heparin is listed in the PDR as Enoxaparin sodium. Interferent test concentrations were determined using treatment of acute ST segment elevation myocardial infarction.

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8.f. FDA: Please explain what CTS Auto-gloss is and why you evaluated this compound as a potential interferent.

BEC Response to Question 8.f.

CTS-Autogloss is a lubricant used by BEC for the blades and/or piercing probes that are used in some of BECs closed tube sampling aliquoters. CTS-Autogloss is tested to ensure that this lubricant does not interfere in the assay. This is not a common substance that customers would encounter, nor will this substance appear as a tested interferent in the IFU.

8.g. FDA: Please also address the item listed in 1d (instrument temperature set points).

BEC Response to Question 8.g.

Please see BEC's response to Question 1.d.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 9: Cross reactivity

FDA: You investigated potential cross reactivity at 18°C, 28°C and NLC (21°C to 25°C). Potential cross-reactive substances were added to plasma pools at 2 concentrations of cTnI (< 0.01 ng/mL and approximately 0.5 ng/mL troponin). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked - mean dose of control)/amount of cross reactant spiked] X 100. You concluded that all percent cross reactivity is less than 1.00%. We are not sure we understand your study and conclusions. Specifically, CKMB and recombinant human troponin T seems to have significantly cross reacted with the assay (please see the table summarizing our review of your data):

Compound	Concentration tested	Temperature	Mean of control	Mean of treated
CKMB	1000 mg/dL	18°C	0.001	1.044
			0.673	1.805
		NLC	0	0.704
			0.654	1.411
		28°C	0	0.583
			0.657	1.292
Recombinant human troponin T	1000 mg/dL	18°C	0.008	0.128
		NLC	0.002	0.136
		28°C	0.002	0.133

9.a. *FDA: While we understand that you evaluated very high concentrations of these compounds, the data provided do not substantiate your claim that the compounds you evaluated did not cross react with the assay. Therefore, please provide additional cross reactivity studies identifying the lowest level of each compound that did not cross-react with the performance of your assay. We recommend that you perform your new studies with a low troponin sample that is closer to the cut-off of your assay and above your LoQ in order to substantiate your cross reactivity claims.*

BEC Response to Question 9.a.

Upon investigation, BEC determined that the CKMB used to perform the cross-reactivity testing for the Submission was from a purified human heart source. Therefore, BEC cannot discount the possibility that material from this source was contaminated with a small amount of TnI. To evaluate this, BEC re-tested CKMB cross-reactivity using a recombinant CKMB source.

Testing was performed at two TnI analyte concentrations (normal ≤ 0.02 ng/mL, and approximately 0.5 ng/mL), at 1000 ng/mL CKMB, at three test temperatures (18 °C, NLC, and 28 °C). The CKMB data are summarized in Table 9-1 below and demonstrate acceptable cross-reactivity.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 9-1: Cross-reactivity Testing Results for Recombinant CKMB at 1000 ng/mL

	cTnI Concentration Normal			cTnI Concentration ~0.5 ng/mL		
Temp °C	cTnI Control Mean, ng/mL	cTnI Test Mean, ng/mL	% Cross-reactivity	cTnI Control Mean, ng/mL	cTnI Test Mean, ng/mL	% Cross-reactivity
18 °C	0.001	0.001	0.000%	0.558	0.564	0.001%
NLC	0.001	0.001	0.000%	0.573	0.564	-0.001%
28 °C	0.001	0.000	0.000%	0.540	0.532	-0.001%

Conclusion: CKMB does not cross-react in the AccuTnI+3 assay, and the elevated results presented in the original Submission were likely a result of contamination of the CKMB material with TnI. No changes are proposed for the product IFU.

Since EP7-A2 recommends that cross-reactivity of an interferent be tested both in the absence (normal sample) and in the presence (~0.5 ng/mL sample) of analyte, BEC did not perform additional testing using a troponin sample closer to the cutoff and above LoQ as performed for interferents. Additional data is found in the TnT cross-reactivity data in Table 9-2, below, where equivalent absolute dose shifts (and therefore cross-reactivity results) are observed for both the normal and positive samples.

BEC repeated the TnT cross-reactivity testing as requested by FDA in the absence (normal sample) and in the presence (0.5 ng/mL) of TnI analyte, at normal laboratory conditions. A dilution series was tested at the following TnT concentrations: 1000, 500, 250, 100, and 50 ng/mL to identify the lowest concentration level that did not cross-react with the assay. The data are summarized in Table 9-2 below.

Table 9-2: TnT Cross-reactivity Testing Results

	TnI Concentration Normal		TnI Concentration ~0.5ng/mL	
TnT Concentration, ng/mL	cTnI Mean Dose, ng/mL	% Cross-reactivity	cTnI Mean Dose, ng/mL	% Cross-reactivity
1000 ng/mL	0.184	0.018%	0.734	0.017%
500 ng/mL	0.085	0.017%	0.655	0.018%
250 ng/mL	0.001	0.000%	0.574	0.003%
100 ng/mL	0.000	0.000%	0.573	0.007%
50 ng/mL	0.000	-0.001%	0.560	-0.013%
0 ng/mL	0.001	N/A	0.566	N/A

Conclusion: While all conditions met the acceptance criteria of percent cross-reactivity less than or equal to 1.00%, there is a dose shift observed when TnT concentrations at or above 500 ng/mL are tested. Therefore, BEC has revised the product IFU to state that no significant cross-reactivity was observed at ≤ 250 ng/mL for TnT.

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9.b. FDA: Please also address the item listed in 1d (instrument temperature set points).

BEC Response to Question 9.b.
Please see BEC's response to Question 1.d.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 10: Precision:

FDA: The precision of the AccuTnI assay was assessed through a series of studies. The first studies are standardized total precision studies performed at 18 °C, 28 °C and NLC (21 °C to 25 °C). The standardized studies at 18 °C and 28 °C were performed internally while the NLC study was performed externally. One instrument and 1 reagent lot was used per study. A single calibration curve was generated at each temperature for each study. A multi-temperature study was also conducted over 14 days, 48 runs at 18 °C, 20 °C, 22 °C, 24 °C, 26 °C and 28 °C (± 2 °C for each temperature setting). One reagent lot and 1 instrument were used for this study. A single calibration curve was generated at 24 °C ± 2 °C. The standardized studies and the multi-temperature study both used 3 commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample and 1 pooled lithium heparin plasma sample. We are concerned that your precision studies may underestimate the imprecision of your assay. Specifically, the multi-temperature study used only 1 instrument and 1 reagent lot.

10.a. FDA: Meanwhile, the standardized study design does not reflect the intended use of this device since the calibration strategy does not reflect the labeled instructions for the assay (see 1b for additional discussion). We recommend that you repeat your precision studies to closely reflect how the end user will utilize this device.

10.b. FDA: We recommend that you include multiple reagent lots, multiple instruments and multiple temperatures closely following the labeled instructions of your assay.

BEC Response to Question 10.a. and Question 10.b.

Two reagent lots and two Access 2 instruments were utilized for the standardized precision studies. While concern was expressed around calibration strategy for the standardized studies, the CLSI EP5-A2 guideline was followed for each of these individual studies. Furthermore, the temperature at which calibration is performed is not a significant contributor to assay imprecision since the AccuTnI+3 calibrator material demonstrates a distinct thermal behavior from patient samples on Access 2. The thermal algorithm is designed to compensate for thermal sensitivity of patient samples. Therefore, the calibration strategy that we used is appropriate for the standardized studies and does not underestimate the imprecision of the assay. For more information on calibration strategies with respect to temperature, see our response to Question 1.b.

While a single reagent lot and instrument were used for the multi-temperature precision study, other studies measured the imprecision of the device across multiple temperatures and utilized additional reagent lots and instruments. These studies included the internal field effectiveness and the multi-temperature LoQ studies. In total, these multi-temperature precision studies encompassed three unique reagent lots and five unique instruments. In all cases, specifications for imprecision were met.

To address the concerns of the Agency, BEC conducted new multi-temperature precision studies on two Access 2 instruments and two reagent lots that were distinct from those of the original multi-temperature precision study. A total of 48 runs were conducted at 18 °C, 20 °C, 22 °C, 24 °C, 26 °C and 28 °C (8 runs at each temperature). The sample set for these new studies included three low-level, natural patient samples. Further, the results were calculated from three different calibration curves, one performed at each of three temperatures (18 °C, 24 °C, and 28 °C). This additional calibration evaluation was performed in order to demonstrate that the temperature at which the calibration is performed does not change the sample concentration, or the imprecision estimate for the assay. The results of these studies are shown below in Table 10-1 and Table 10-2.

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Table 10-1: Instrument #1 - Results of New Multi-temperature Precision Studies

Instrument #1, Lot #1		18 °C Calibration Curve			24 °C Calibration Curve			28 °C Calibration Curve		
Sample	n	Mean, ng/mL	Total SD	Total CV	Mean, ng/mL	Total SD	Total CV	Mean, ng/mL	Total SD	Total CV
Pr 1	96	0.042	0.0023	5%	0.039	0.0023	6%	0.039	0.0023	6%
Pr 2	96	0.433	0.0160	4%	0.435	0.0161	4%	0.435	0.0157	4%
Pr 3	96	1.014	0.0269	3%	1.017	0.0270	3%	1.014	0.0265	3%

Table 10-2: Instrument #2 - Results of New Multi-temperature Precision Studies

Instrument #2, Lot #2		18 °C Calibration Curve			24 °C Calibration Curve			28 °C Calibration Curve		
Sample	n	Mean, ng/mL	Total SD	Total CV	Mean, ng/mL	Total SD	Total CV	Mean, ng/mL	Total SD	Total CV
Pr 1	96	0.044	0.0023	5%	0.039	0.0022	6%	0.040	0.0023	6%
Pr 2	96	0.427	0.0212	5%	0.412	0.0212	5%	0.428	0.0221	5%
Pr 3	96	1.002	0.0467	5%	0.978	0.0469	5%	1.021	0.0497	5%

Conclusion: All acceptance criteria were met for all samples at each calibration condition (for doses > 0.105 ng/mL, %CV ≤ 8%; for doses ≤ 0.105 ng/mL, SD ≤ 0.0084 ng/mL). Further, imprecision was not impacted by the calibration temperature, and no concentration bias was observed across the three calibration conditions, reagent lots, or instruments.

Additional analysis:

To further demonstrate the effectiveness of the algorithm, the imprecision for each of the three samples run in the multi-temperature study above was also calculated *without* the algorithm applied (before algorithm), and the results compared to those *with* the algorithm applied (after algorithm). Since calibration temperature does not impact imprecision measurements, as illustrated in the tables above, the 24 °C calibration curve was selected to calculate the imprecision measurements. The results of these calculations are shown below in Table 10-3 and Table 10-4.

Table 10-3: Instrument #1 - Assay Imprecision Before and After Application of the Thermal Algorithm

Instrument #1, Lot #1		Before Algorithm				After Algorithm			
Sample	n	Mean, ng/mL	Within Run CV	Between Run CV	Total CV	Mean, ng/mL	Within Run CV	Between Run CV	Total CV
Pr 1	96	0.036	6%	19%	20%	0.039	5%	4%	6%
Pr 2	96	0.436	2%	15%	15%	0.435	2%	3%	4%
Pr 3	96	1.017	2%	13%	14%	1.017	2%	2%	3%

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Table 10-4: Instrument #2 - Assay Imprecision Before and After Application of the Thermal Algorithm

Instrument #2, Lot #2		Before Algorithm				After Algorithm			
Sample	**n**	**Mean, ng/mL**	**Within Run CV**	**Between Run CV**	**Total CV**	**Mean, ng/mL**	**Within Run CV**	**Between Run CV**	**Total CV**
Pr 1	96	0.036	4%	19%	19%	0.039	4%	5%	6%
Pr 2	96	0.419	3%	15%	16%	0.412	3%	4%	5%
Pr 3	96	0.992	3%	14%	14%	0.978	3%	4%	5%

Conclusion: The algorithm provides a substantial improvement in imprecision when a study is executed across multiple temperatures. Specifically, the improvement in the "Between Run" component of imprecision (which is synonymous with "Between Temperature" imprecision based on the study design) demonstrates the effectiveness of the algorithm.

10.c. FDA: You should also include a natural (unmodified) low-level patient sample with troponin values close to your cut-offs in order to determine the imprecision of your device on natural patient samples at the medical decision points.

BEC Response to Question 10.c.

Natural, low-level patient samples with troponin I values close to the cut-offs were used for all LoQ studies. While the LoQ study provides a robust estimate of imprecision, BEC also recognizes that the study design is distinct from EP5-A2.

To address the concerns of the Agency, two additional multi-temperature precision studies were performed to evaluate the precision of low-level, natural patient samples. See data in our response to Question 10.a. and 10.b., above.

10.d. FDA: Please also address the issue identified in 1d (instrument temperature set points).

BEC Response to Question 10.d.

Please see BEC's response to Question 1.d.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 11: HAMA/Heterophile antibody interference studies:

FDA: You performed testing using a control reagent pack with the conjugate formulation containing blockers and a test reagent pack where the formulation did not contain blockers using 45 suspected HAMA or heterophile samples. The relative light unit output and doses were compared for the suspected HAMA/heterophile interferent samples from both the test and control pack. Your acceptance criterion is defined as "this study is intended to characterize blocker effectiveness." You conclude that all samples with insignificant, moderate and high reactivity were effectively suppressed by the blocking agents. We are not sure we understand your study. Specifically, you do not seem to have a predetermined performance goal to define no interference. Therefore, please provide a summary table of the doses obtained with the control and test reagents. Please also clearly define the performance goal that you pre-defined as demonstrating no interference from HAMA/heterophile antibodies and provide evidence that you have met your pre-determined performance goals.

BEC Response to Question 11.

Heterophile, including human-anti-mouse antibody (HAMA), interference in immunoassay systems is a known limitation of antibody-based technology. The blockers utilized in the AccuTnI+3 assay have been formulated to be effective against known heterophilic interference. Despite the presence of blockers, the possibility exists that interfering antibodies in an individual patient may cause erroneously elevated results. Therefore, a warning, consistent with the standard approach in the IVD industry for HAMA/heterophile labeling, is included in the Limitations of the Procedure section of the Instructions for Use:

> *"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."*

The predetermined qualitative performance goal was to "characterize blocker effectiveness". BEC did not have a predetermined "quantitative" performance goal for heterophile interference. Because the heterophile interference is very formulation-specific, patient samples containing known interferents for one assay or assay formulation may not interfere in another assay or assay formulation. Therefore, acquiring and using an uncharacterized panel of interfering samples with a quantitative specification of "less than a certain frequency of interference" would not be informative. The input specification to "characterize blocker effectiveness" was intended to address the specific study design, where a panel of suspected interfering samples is tested with and without the assay's blockers present in the reaction. For the AccuTnI+3 assay, the expectation (and its only specification) is that specimens containing heterophile interferents and tested with the AccuTnI+3 formulation *without blockers* will demonstrate interference (erroneously elevated signal), while the same specimens tested with an assay formulation *with blockers* will demonstrate reduced interference (reduced signal).

Table 11-1 below shows the results for each sample. In the chart, "Control" indicates results with blockers present, and "Test" indicates results with blockers removed from the reagent pack components.

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Table 11-1: Results of Heterophile Testing in AccuTnI+3, With and Without Blockers

Samples	Control Mean RLU	Control Dose (ng/mL)	Test Mean RLU	Test Dose (ng/mL)	RLU Control vs. Test % Difference
VF-05589	443051	1.48	445673	1.39	-0.6%
N36653	40673	0.10	40934	0.10	-0.6%
S09499#46	13603	0.00	14119	0.00	-3.8%
N36665	13190	0.00	13899	0.00	-5.4%
N36694	13800	0.00	14737	0.01	-6.8%
S09637	12716	0.00	13650	0.00	-7.3%
S09978 #92	15742	0.01	16910	0.02	-7.4%
S11621	13550	0.00	14586	0.00	-7.6%
CP19SEP88	20958	0.03	22569	0.04	-7.7%
LP86424 11/12/02	13791	0.00	15238	0.01	-10.5%
VF-06935	12538	0.00	14028	0.00	-11.9%
N28755	13066	0.00	14645	0.00	-12.1%
N31446	13483	0.00	15114	0.01	-12.1%
S09842	13684	0.00	15401	0.01	-12.5%
FG79842	13892	0.00	15642	0.01	-12.6%
N28755	14141	0.00	15944	0.01	-12.8%
SF04393	13623	0.00	15520	0.01	-13.9%
S11589	13985	0.00	15998	0.01	-14.4%
86402	13272	0.00	15338	0.01	-15.6%
N44314	13084	0.00	15122	0.01	-15.6%
AD 1-91-89	13985	0.00	16288	0.01	-16.5%
N36688	13764	0.00	16117	0.01	-17.1%
S11618 #51	13246	0.00	15593	0.01	-17.7%
19843	13080	0.00	15715	0.01	-20.1%
LP86450	15926	0.01	19486	0.03	-22.4%
VF-06274	13774	0.00	17060	0.02	-23.9%
SF-02855	13760	0.00	17374	0.02	-26.3%
LP77328	13082	0.00	17291	0.02	-32.2%
19857	12638	0.00	17399	0.02	-37.7%
VF-06347	215728	0.73	297829	0.96	-38.1%
VF-07517	16549	0.02	22962	0.04	-38.7%
580827-0333	13175	0.00	18665	0.02	-41.7%
19848	12894	0.00	18916	0.03	-46.7%
19862	13324	0.00	25496	0.05	-91.4%
19860	12264	0.00	23849	0.04	-94.5%
19865	12134	0.00	25485	0.05	-110.0%
S09743 #34	12352	0.00	26747	0.05	-116.5%
19861	12457	0.00	26991	0.05	-116.7%
19847	12579	0.00	40821	0.10	-224.5%
19850	18842	0.03	85239	0.25	-352.4%
S09860 #64	13352	0.00	63568	0.18	-376.1%
RF17I26609	14527	0.01	106366	0.32	-632.2%
LP86256 11/7/02	13152	0.00	127634	0.40	-870.5%
19859	12881	0.00	142935	0.44	-1009.6%
N41527	13298	0.00	152401	0.47	-1046.0%

As described in the Submission, 12 of the 45 heterophile samples tested demonstrated significant interference without blockers, with >100% reduction in signal (relative light units, or "RLU"), 15 of 45 demonstrated moderate interference (15 - 50% reduction in signal), and despite their categorization as "known heterophile samples," 18 of 45 demonstrated minimal interference (< 15% signal reduction).

Since the cardiac status of the subjects who provided the samples is unknown, we are unable to directly link disease state with sample TnI values. However, one would expect the blockers to effectively reduce any interference to less than the 99th percentile URL (0.02 ng/mL) in samples from normal subjects. Twenty

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samples (indicated in the table in red) went from above the cutoff (≥ 0.02 ng/mL) to below the cutoff (< 0.02 ng/mL) with addition of blockers, demonstrating blocker effectiveness. An additional 20 samples (indicated in the table in blue) were negative for troponin (< 0.02 ng/mL) both with and without blockers, indicating that any interference these samples may have exerted in conjunction with the AccuTnI+3 assay or its blockers did not result in signal elevation. Of the remaining 5 samples (indicated in the table in black), two were positive for troponin (> 0.02 ng/mL), and the blockers showed no reduction in signal, indicating that these samples did not contain interferents for the AccuTnI+3 assay; the other three samples showed a signal decrease with the blockers but remained above the cutoff, indicating that both troponin and interferent were present.

Based on these data, BEC concluded that the blocker formula used in the AccuTnI+3 reagent formulation is effective in reducing or eliminating the effects of interferents that could lead to false positive results. However, the cautionary statement regarding HAMA/heterophile interference will remain in the Limitations for Use section of the device IFU.

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Question 12: Analytical Matrix Comparison Studies

12.a. FDA: Please explain what features of the data led you to choose Passing-Bablok as opposed to, for example, Deming regression. How does the imprecision differ between the 2 matrices?

BEC Response to Question 12.a.

The Passing-Bablok method provides a robust slope estimate that is not skewed by a small number of influential data points. The typical distribution of TnI concentrations is highly skewed toward low concentrations, making the less frequent high concentration samples overly influential in a Deming regression. Therefore, in our original analysis, the acceptance criteria as stated in our Design Input Document were based on the Passing-Bablok slope (Passing-Bablok slope = 1.00 ± 0.10). Therefore, no alternative analyses were performed on the data included with the Submission.

Estimates of imprecision between the two sample types (lithium heparin plasma and serum) had not been previously calculated. BEC calculated individual sample imprecision (%CVs) at each test temperature by sample type. A sign test was performed comparing the imprecision between each sample pair (lithium heparin vs. serum) at each temperature, and indicates no significant difference in imprecision between sample types. The data are provided in Table 12-1 below.

Table 12-1: Precision of AccuTnI+3, by Sample Matrix and by Temperature

Sample Type	Temperature	Average % CV	Median % CV	Replicate Diff	N	p
Lithium Heparin	18°C	2.4%	1.5%	Serum<LiHep	51	1.000
Serum		2.1%	1.6%	Serum>LiHep	52	
Lithium Heparin	23°C	2.3%	1.4%	Serum<LiHep	55	0.555
Serum		2.1%	1.2%	Serum>LiHep	48	
Lithium Heparin	28°C	2.3%	1.5%	Serum<LiHep	48	0.555
Serum		2.4%	1.3%	Serum>LiHep	55	

There is no statistically significant difference in imprecision between sample types at different temperatures.

12.b. FDA: Please also address the item listed in 1d (instrument temperature set points).

BEC Response to Question 12.b.

See our response in 1.d

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(b)(4)

[redacted]

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(b)(4)

[redacted]

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Question 14: DxI Instrument

FDA: The purpose of Appendix 5 is described as "this document contains generalized requirements for thermal monitoring on both Access 2 and DxI." Appendix 10 also discusses software requirements for the DxI instrument. Meanwhile Appendix 13 page 5 states "since this implementation was done on DxI originally and fully verified before being merged to Access 2, only performing regression unit tests." On page 8 of Appendix 13 you state "run regression tests on merged code from DxI." On page 94 of appendix 14 you list "merged from DxI: Load new APF thermal data." On page 103 of Appendix 14 you list "merge AP XML schema definition (XSD) file from DxI branch." On page 120 of appendix 14 you list "merge thermal correction database updates from DxI to Access 2 XP." We have the following recommendation and comment:

14.a. FDA: All software verification and validation activities should be fully performed on the Access 2 instrument in order to market this instrument with this software.

BEC Response to Question 14.a.

BEC confirms that all software verification and validation activities related to this submission were fully performed on the Access 2 instrument.

The Submission contained multiple references to the DxI platform because some of the original system software development work was done on DxI, and then the identical code was used for Access 2 system software version 3.3. The finished Access 2 system software version 3.3 has undergone full verification and validation on the Access 2 instrument.

14.b. FDA: In the current submission, we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay System.

BEC Response to Question 14.b.

Question 14.b. is an information-only statement from FDA. No response is required.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 15: Additional software

FDA: Appendix 7, 8, 9 and 10 discuss the NexStep configuration. This is described as a "configuration of Access instruments that allows the laboratory to network several Access instruments together to manage the instrument data, both results, supplies and set-up information from on PC." Please be advised that in the current submission we have only reviewed the testing for Access AccuTnI on the Access 2 Immunoassay Systems using Access 2 3.3 software.

BEC Response to Question 15.

We understand that FDA has only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay Systems using Access 2 3.3 software.

Question 15 is an information-only statement from FDA. No additional response is required.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 16: IUO and IVD builds

FDA: On page 9 of Appendix 15 you state that selected Access 2 test procedures will be verified on the IVD version. The IVD version contains changes to update Help and language string files. The IVD systems software CD also has the ability to auto detect the operating system on which the software is being installed and automatically installs the correct package for targeted operating system. Please note that you should verify and validate the exact IVD software version that you intend to market. If you used the IUO software version in any of the clinical studies (reference interval trial, pivotal efficacy trial and matrix comparison trial), please justify why you believe validating the IU[O] software version also validates the clinical performance of the IVD software.

BEC Response to Question 16.

The Access 2 system software version 3.3 is identical between the IUO and IVD builds (installation CDs). The IVD build includes Access 2 system software version 3.3 and additional files and utilities not contained in the IUO version, but required to support the full worldwide release of the software. These additional files include help files, language strings files, and installation utilities. Help files, language strings files, and the installation utility are completely separate from the Access 2 system software, and the system software source code was not modified between the IUO and IVD builds. In addition:

- ◊ The IVD build removed the terminology "For Investigational Use Only" from screens that were present in the IUO build.
- ◊ The system is structured so the contents of the help files and the text on the user interface screen can be updated without the need to modify the system software code.
- ◊ The change to the installation utility (between the IUO build and the IVD build) provides the capability to install the exact same system software on either Windows NT-based or Windows XP-based Console computers.

Any modifications peripheral to the system software, such as help files, language strings files, and the installation utility, were verified and validated with the final IVD system software CD. These do not impact the operation of the device nor impact the established clinical performance.

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Question 17: Hardware

FDA: On Page 7-2 you state "The case temperature sensor (thermistor) is the critical hardware component used to detect small changes in temperature, and has an accuracy specification of ± 0.2°C. This specification of ± 0.2°C was 100% verified by the supplier. Manufacturing release procedures for new instruments ensure that verified thermistors are installed." You will need to ensure that all instruments running this assay have the verified thermistors installed.

BEC Response to Question 17.

BEC will ensure that all Access 2 instruments running AccuTnI+3 have the verified thermistors installed.

- ◊ All Access 2 instruments manufactured since January 24, 2012 include the verified case temperature sensor (thermistor.)
- ◊ In April, 2012 BEC initiated a hardware modification program to replace the thermistors in all fielded Access 2 systems. As of November 29, 2012, BEC has completed the hardware modification on 71% of the Access 2 instruments installed in the United States.
- ◊ BEC will ensure that the modifications are complete before customers can install and run the AccuTnI+3 assay.

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Question 18: Stability studies

FDA: Five studies were conducted to assess the stability of the Access AccuTnI reagent and calibration materials. We have the following concerns and recommendations:

18.a. FDA: Reagent pack real time stability: For the reagent pack real time stability, at each time point the mean value of each control was calculated. From this mean value a "Z" value was calculated as follows: Z = (observed dose-stated dose)/expected SD. You base your acceptance criteria on the Z value. For normal patient samples, all values must be ≤ 0.04 ng/mL. We do not understand why the Z value is used as the acceptance criteria. Please explain the significance of the Z value and why it is appropriate to demonstrate acceptable stability for the control samples. We also do not understand why normal patient samples should be ≤ 0.04 ng/mL. It seems that normal patient samples should be less than the established 99th percentile of the normal population. Therefore, we have the following recommendations:

18.a.i. FDA: We recommend that you add acceptance criteria for the precision and accuracy of each control sample at each time-point compared to time-point 0. Please keep in mind that since calculating means can potentially mask big differences in the performance of individual replicates, we do not believe that acceptable stability should be based on means. All replicates should fall within your pre-determined acceptance criteria.

BEC Response to Question 18.a. and 18.a.i.

Significance of Z-value

The Z-value is used as the acceptance criteria in reagent pack and calibrator real-time stability to normalize sample acceptance criteria for multiple concentrations across the assay range. The Z-value (Z = (observed dose-stated dose)/expected SD) is derived using the total variability estimation.

The following factors are incorporated into the acceptance criteria for each time point:

◊ The assay capability characterization which includes variation caused by replicate, run, day, instrument, calibration, reagent pack, calibrator pack and operator provides the expected SD and CV inputs to the Z-value equation.

This approach is in line with the design of the real-time stability protocol as it includes multiple instruments, calibrations, days, operators and consumables throughout the course of the study.

◊ The control value assignment incorporates targets for accuracy and estimates of precision at specific dose ranges, and subsequently are the expectations for the average result for each control sampled at a specific time point.

Specification for Normal Samples:

The specification for normal samples was set at 0.04 ng/mL based on current commercial AccuTnI product's URL, as URL for the new product had not yet been established at the time of pilot production. Upon completion of verification and validation, the URL was established and subsequently the acceptance criterion for normal samples was revised to be consistent with the established claim of the 99th percentile of normal population (0.02 ng/mL). The results from all lots were reanalyzed and met this new specification.

Acceptance Criteria for Individual Samples:

Real-time stability results were presented based on samples means in compliance with our established protocols. At the time of the submission, this study was on-going and data was only presented out to six months. Since that time, the study has been completed out to 12 months and this full dataset is now

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provided below.

The data submitted in support of our reagent real-time stability were generated under our established real-time stability protocol and analysis process. The predetermined acceptance criterion for this study considers the following:

◊ Each individual control must first meet the individual control acceptance criteria as compared to target.
◊ The average of each individual control is translated into a Z-value as described above (Z = (observed dose-stated dose)/expected SD).
◊ Acceptability is determined based on the mean of the Z of all controls as compared to baseline.

The following acceptance criteria (Table 18-1) have been established for the evaluation of the data generated for real-time stability presented in the tables below.

Table 18-1: Real-time Stability Acceptance Criteria

Control Evaluation	Acceptance Criteria
Individual replicates within reference interval	≤ 10 replicates outside 3Z
Individual controls from baseline	2Z
Average of all controls from baseline	1Z

In the Submission, reagent pack real-time stability data were presented for six months. Additional time points are now complete and are included in the evaluation summarized in Table 18-2, Table 18-3, and Table 18-4 below.

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Table 18-2: Reagent Pack Real-Time Stability Results, Lot 116676

Reagent Pack Real Time Stability Results, Lot 116676								
Time Point	**Baseline**	**3 Months**	**4 Months**	**6 Months**	**9 Months**	**12 Months**	**13 Months**	
	Mean (ng/mL)	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	
Mean Control Values								**Stated Values (ng/mL)**
Control 1	0.056	0.059	0.062	0.058	0.066	0.057	0.055	0.035-0.079
Control 2	0.798	0.746	0.789	0.738	0.820	0.716	0.685	0.619-0.855
Control 3	3.85	3.656	3.853	3.48	3.844	3.269	3.271	2.961-4.088
Control 4	0.026	0.035	0.031	0.036	0.032	0.028	0.031	0.008-0.052
Control 5	1.086	1.11	1.123	1.032	1.104	0.938	0.946	0.842-1.163
Control 6	15.643	15.694	16.023	14.937	15.603	14.093	13.655	12.402-17.127
Control Mean Z Values								**Specification**
Control 1	-0.09	0.19	0.49	0.11	0.79	0.64	0.43	±2.00 Z
Control 2	1.03	0.15	0.89	0.02	1.40	0.53	0.07	±2.00 Z
Control 3	1.16	0.47	1.17	-0.16	1.14	0.12	-0.25	±2.00 Z
Control 4	-0.37	0.47	0.12	0.53	0.19	0.33	0.29	±2.00 Z
Control 5	1.03	1.33	1.49	0.36	1.26	0.45	0.06	±2.00 Z
Control 6	0.74	0.79	1.07	0.15	0.71	0.17	-0.21	±2.00 Z
Overall Mean Z	0.58	0.57	0.87	0.17	0.91	0.37	0.07	±2.00 Z
Z from Baseline	[redacted]	-0.01	0.29	-0.14	0.33	-0.21	-0.51	±1.00 Z
Pass/Fail	[redacted]	Pass	Pass	Pass	Pass	Pass	Pass	[redacted]
[redacted]								
Individual Assay Normal Patient Results								[redacted]
Patient 0	Pass	Pass	Pass	Pass	Pass	Pass	Pass	All results ≤0.02 ng/mL
Patient 1	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	Pass	Pass	Pass	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 18-3: Reagent Pack Real-Time Stability Results, Lot 116677

Reagent Pack Real Time Stability Results, Lot 116677								
Time Point	Baseline	3 Months	4 Months	6 Months	9 Months	12 Months	13 Months	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values								**Stated Values (ng/mL)**
Control 1	0.053	0.059	0.062	0.057	0.062	0.055	0.054	0.035-0.079
Control 2	0.748	0.768	0.780	0.720	0.766	0.692	0.671	0.619-0.855
Control 3	3.646	3.812	3.694	3.275	3.734	3.271	3.150	2.961-4.088
Control 4	0.024	0.035	0.034	0.029	0.028	0.025	0.027	0.008-0.052
Control 5	1.016	1.098	1.090	1.018	0.986	0.910	0.890	0.842-1.163
Control 6	14.669	15.333	15.167	14.217	14.686	13.662	13.161	12.402-17.127
Control Mean Z Values								**Specification**
Control 1	-0.34	0.19	0.45	-0.04	0.42	-0.14	-0.26	±2.00 Z
Control 2	0.19	0.53	0.74	-0.30	0.49	-0.77	-1.12	±2.00 Z
Control 3	0.43	1.02	0.60	-0.88	0.74	-0.90	-1.33	±2.00 Z
Control 4	-0.51	0.44	0.37	-0.07	-0.20	-0.43	-0.31	±2.00 Z
Control 5	0.16	1.18	1.08	0.19	-0.22	-1.16	-1.41	±2.00 Z
Control 6	-0.08	0.48	0.34	-0.46	-0.07	-0.93	-1.36	±2.00 Z
Overall Mean Z	-0.03	0.64	0.60	-0.26	0.20	-0.72	-0.97	±2.00 Z
Z from Baseline		0.67	0.63	-0.23	0.23	-0.69	-0.94	±1.00 Z
Pass/Fail		Pass	Pass	Pass	Pass	Pass	Pass	
Individual Assay Normal Patient Results								
Patient 1	Pass	Pass	Pass	Pass	Pass	Pass	Pass	All results ≤0.02 ng/mL
Patient 2	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Patient 3	Pass	Pass	Pass	Pass	Pass	Pass	Pass	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 18-4: Reagent Pack Real-Time Stability Results, Lot 116678

Reagent Pack Real Time Stability Results, Lot 116678											
Time Point	Baseline	3 Month	4 Month	6 Month	7 Month	9 Month	10 Month	11 Month	12 Month	13 Month	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values											**Stated Values (ng/mL)**
Control 1	0.055	0.058	0.060	0.054	0.060	0.057	0.057	0.057	0.053	0.056	0.035-0.079
Control 2	0.771	0.756	0.758	0.690	0.717	0.734	0.688	0.676	0.660	0.690	0.619-0.855
Control 3	3.750	3.665	3.569	3.304	3.355	3.466	3.209	3.170	3.200	3.247	2.961-4.088
Control 4	0.027	0.031	0.034	0.028	0.030	0.028	0.027	0.027	0.028	0.030	0.008-0.052
Control 5	1.074	1.089	1.072	1.004	1.008	1.001	0.978	0.960	0.924	0.959	0.842-1.163
Control 6	15.599	15.200	15.197	14.614	14.724	14.062	14.144	13.469	13.717	13.556	12.402-17.127
Mean Control Values											**Specification**
Control 1	-0.15	0.11	0.25	-0.32	0.25	-0.02	-0.04	0.03	-0.36	-0.06	±2.00 Z
Control 2	0.58	0.33	0.36	-0.80	-0.34	-0.05	-0.82	-0.86	-1.31	-0.79	±2.00 Z
Control 3	0.80	0.50	0.16	-0.78	-0.60	-0.21	-1.12	-1.17	-1.15	-0.98	±2.00 Z
Control 4	-0.31	0.07	0.38	-0.16	-0.04	-0.18	-0.28	-0.12	-0.22	0.00	±2.00 Z
Control 5	0.88	1.07	0.86	0.01	0.07	-0.02	-0.31	-0.39	-0.99	-0.54	±2.00 Z
Control 6	0.71	0.37	0.37	-0.13	-0.03	-0.59	-0.53	-0.82	-0.89	-1.02	±2.00 Z
Overall Mean Z	0.42	0.41	0.40	-0.36	-0.12	-0.18	-0.52	-0.56	-0.81	-0.57	±2.00 Z
Z from Baseline	[redacted]	-0.01	-0.02	-0.78	-0.54	-0.60	-0.94	-0.98	-1.23	-0.99	±1.00 Z
Pass/Fail	[redacted]	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Fail	Pass	[redacted]
[redacted]											
Individual Assay Normal Patient Results											
Patient 1	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	All results ≤0.02 ng/mL
Patient 2	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Patient 3	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	

In addition to our standard analysis of the real-time stability data, Beckman Coulter performed additional analysis of the data to address the Agency's concerns that the analysis was assessed on the means of replicates and not on individual replicates.

In establishing the acceptance criteria for individual control sample replicates at each time point, the total replicates achieved across the study were considered. Given the three standard deviation (3 SD) acceptance interval for individual replicates, the expected probability of having a replicate outside this interval is 0.0027. Using the total number of replicates in the real-time stability protocols (3895 total individual replicates), we have established an expected incidence rate of ≤10 replicates outside of the acceptance interval given a normal distribution of data (3895 total replicates * 0.0027 interval of 3 SD = 10.52 replicate incidence rate).

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Results of individual replicate evaluation are presented in Table 18-5 below. Graphs of individual controls with all replicates are provided in Appendix 7.

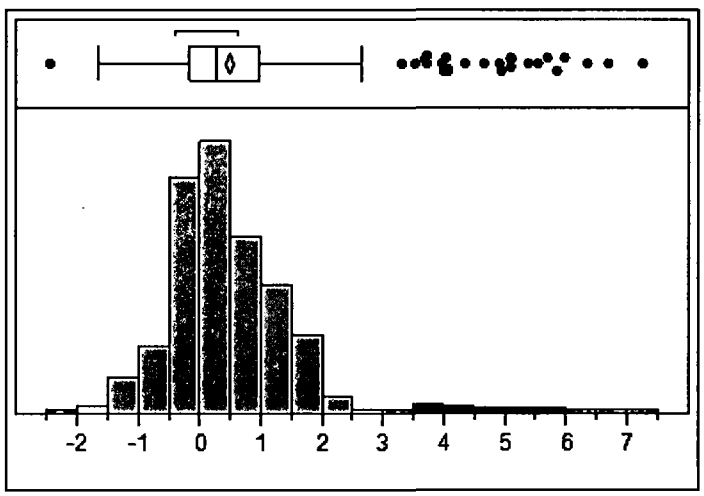
Table 18-5: Results of Individual Replicate Evaluation

	Lot	Replicates Outside Interval	Acceptance Criteria	
Reagent Pack	116676	1*	[redacted]	
	116677	1		
	116678	0		
Total Replicates Outside Interval (*excluding outliers)		2	≤10	PASS

*See the following paragraph and Figure 18-1for a discussion of outliers.

There was one run of reagent pack lot 116676 on day 224 in which all replicates of 5 controls assessed were outside of the acceptance interval. This run is believed to be an outlier based on Boxplot analysis of the data (see table below) and is not indicative of reagent instability. These replicates are considered outliers and not within the expected random variability based on overall sample size.

Figure 18-1: Potential Outliers Based on Boxplot on Pack 116676



Conclusion: The analysis of individual controls provides the same conclusions as our original evaluation of the replicate means, in that the data generated supports a 12-month shelf life for the AccuTnI+3 reagents.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

18.a.ii. FDA: Please make sure that you base your new acceptance criteria on the medical needs of this assay.

BEC Response to Question 18.a.ii.

These acceptance criteria best represent the known total multi-factorial error at different doses, and estimated precision and accuracy for each control sampled; therefore we accept this Z-value as an acceptance criteria based on medical need.

18.b. FDA: Reagent Open Pack Stability: In order to determine acceptable open pack stability, mean doses for each sample at each time point were calculated. For samples ≤0.105 ng/mL, doses were scaled according to ±125% of the expected SD to allow all data to be combined for analysis. Mean doses were platted versus time and compared to baseline values. The best fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. As discussed above, we do not concur with acceptance criteria based on mean. Furthermore we do not concur with scaling doses according to the expected SD. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

BEC Response to Question 18.b.

Reagent open pack stability results were presented based on sample means following recommendations from EP25-A "Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline." The scaling of the low-dose sample was performed so that all samples could be combined into one analysis. The predetermined acceptance criteria for this study were:

◊ Best fit line through all controls and time points at maximum time point (≥ 35 days) must be ± 10.0 % of line fit at baseline for samples >0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ± 125% of the expected SD (0.0084 ng/mL) specification will be applied.

The 10% specification was developed as follows: A Monte Carlo study, assuming 5% difference is acceptable and an expected imprecision of 8%, provided an additional 5% variability of a regression estimate such that a percent difference specification of ± 10% gives 5% type I error. This ratio of specification to imprecision (10%/8% = 125%) was carried over to the difference specification for low concentration samples.

Based on the recommendation of the Agency, additional study criteria were developed for evaluating individual sample regressions, and individual replicates:

◊ Best fit line through all replicates of individual controls at maximum time point (≥ 35 days) must be ±10.0 % of line fit at baseline for samples >0.105 ng/mL. For individual samples ≤ 0.105 ng/mL, a ± 125% of the expected SD (0.0084 ng/mL) specification will be applied (0.0105 ng/mL).

◊ All replicates must be ±3 SD (±24%) of the baseline mean dose for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, all replicates must be ± 0.0252 (3 SD) of the baseline mean dose.

To address the concerns of the Agency, BEC has re-calculated these stability results, by sample, using individual replicates. In addition, the low sample results (QCPT1) are presented below without the scaling included in the originally submitted data. The same criteria (±10.0 % or ± 0.0105 ng/mL depending on sample concentration) was applied to individual samples as was applied to the mean of all samples, ensuring acceptable stability was achieved at each target concentration and that there was not an underlying stability issue being masked by the previous analysis approach. Using a 3SD criterion for individual replicates gives a probability of 0.0027 that any given replicate during the study would be outside the study; given the

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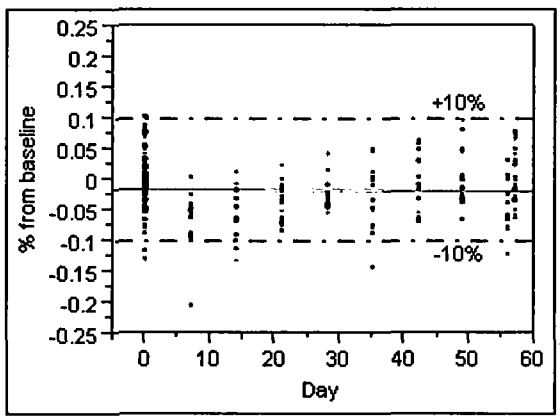
Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

sample size in the study (N = 250), no more than 1 replicate would be expected to be outside this specification. The charts below demonstrate that no individual replicates were outside of the 3 SD range. BEC did not have pre-defined acceptance criteria for imprecision for stability studies. However, based on the individual sample plots (Figure 18-3, Figure 18-4, Figure 18-5, and Figure 18-6) no imprecision degradation was observed over time. Additionally, all individual replicates met the expected 3 SD range.

Overall Conclusion: These updated stability analyses support the claim that the AccuTnI+3 open reagent pack is stable for 56 days.

The following graphs (Figure 18-2, Figure 18-3, Figure 18-4, Figure 18-5, and Figure 18-6) represent the Reagent Open Pack stability data using individual sample replicates. The first graph includes the combination of all samples, and the subsequent graphs are for individual samples. The regression lines and standard deviation ranges are noted on each graph.

Figure 18-2: Open Pack Stability: Bivariate Fit of % from baseline By Day – All Replicates and Samples Combined



Linear Fit: % from baseline = -0.015937 - 4.4843e-5*Day

Conclusion: When all replicates for all samples are combined, the linear regression meets the ± 10% specification for the open reagent pack stability study to 56 days.

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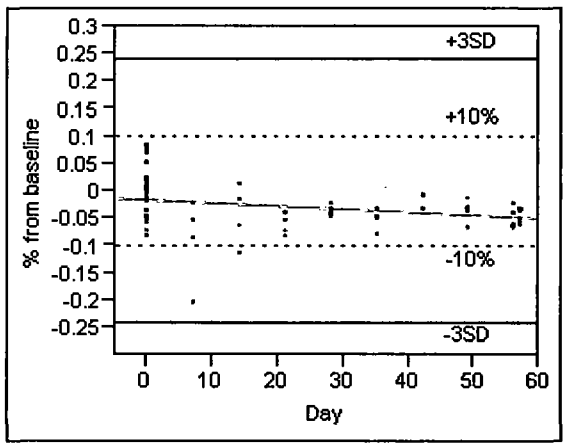
Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

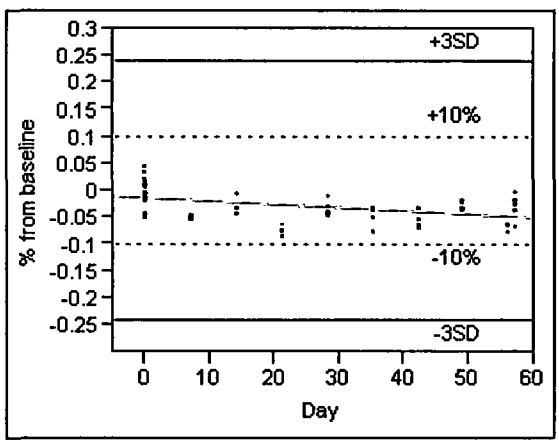
Figure 18-3: Open Pack Stability: Bivariate Fit of % from baseline By Day Sample Name = Cardiac MORE 2



Linear Fit: % from baseline = -0.017762 - 0.0005589*Day

Conclusion: For the sample Cardiac More 2 (mean dose = 1.00 ng/mL), the linear regression meets the ± 10% criteria for the open reagent pack stability study to 56 days. Additionally, all individual replicates meet the ± 3SD criteria.

Figure 18-4: Open Pack Stability Bivariate Fit of % from baseline By Day Sample Name = Cardiac MORE 3



Linear Fit: % from baseline = -0.012621 - 0.0006413*Day

Conclusion: For the sample Cardiac More 3 (mean dose = 14.15 ng/mL), the linear regression meets the 10% criteria for the open reagent pack stability study to 56 days. Additionally, all individual replicates meet the ±3 SD criteria.

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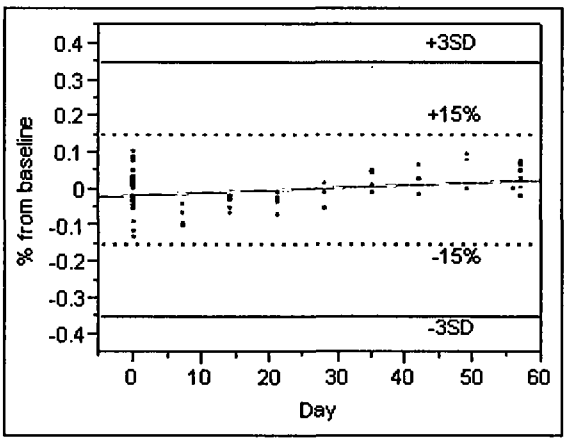
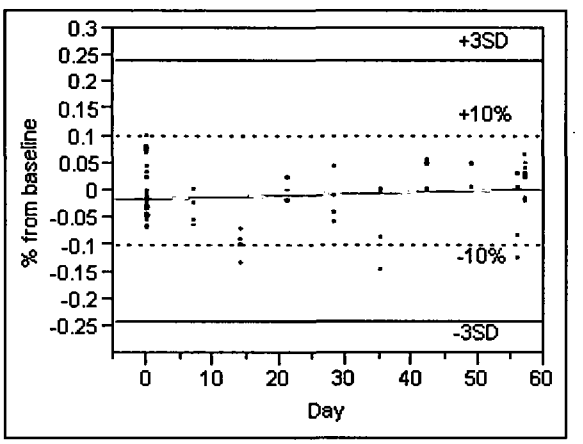
Figure 18-5: Open Pack Stability Bivariate Fit of % from baseline By Day Sample Name=TnI QCPT1



Linear Fit: % from baseline = -0.017525 + 0.0007109*Day

Conclusion: For the sample QCPT1 (mean dose = 0.071 ng/mL), the linear regression meets the ± 0.0105 ng/mL (± 15% based on concentration) criteria for the open reagent pack stability study to 56 days. Additionally, all individual replicates meet the ± 3 SD criteria.

Figure 18-6: Open Pack Stability Bivariate Fit of % from baseline By Day Sample Name=TnI QCPT2B



Linear Fit: % from baseline = -0.015792 + 0.0003089*Day

Conclusion: For the sample QCPT2B (mean dose = 41.55 ng/mL), the linear regression meets the ± 10% criteria for the open reagent pack stability study to 56 days. Additionally, all individual replicates meet the ± 3 SD criteria.

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18.c. FDA: Stored Calibration Curve Stability: In order to verify the 56 day stability of the stored calibration curve, mean doses for each sample at each time point were calculated. For samples ≤ 0.105 ng/mL, doses were scaled according to ± 125% of the expected SD. Mean doses were plotted versus time and compared to baseline values. The best fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. As discussed above, we do not concur with acceptance criteria based on mean and we do not concur with scaling doses according to the expected SD. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

BEC Response to Question 18.c.

Reagent calibration curve stability results were presented based on samples means following recommendations from EP25-A. The scaling of the low-dose sample was performed so that all samples could be combined into one analysis. The predetermined acceptance criteria for this study were:

◊ Best fit line through all controls and time points at maximum time point (≥ 35 days) must be ±10.0 % of line fit at baseline for samples >0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ± 125% of the expected SD (0.0084 ng/mL) specification will be applied.

The 10% specification was developed as follows: A Monte Carlo study, assuming 5% difference is acceptable and an expected imprecision of 8%, provided an additional 5% variability of a regression estimate such that a percent difference specification of ±10% gives 5% type I error. This ratio of specification to imprecision (10%/8% = 125%) was carried over to the difference specification for low concentration samples.

Based on the recommendation of the Agency, additional study criteria were developed for evaluating individual sample regressions, and individual replicates:

◊ Best fit line through all replicates of individual controls at maximum timepoint (≥ 35 days) must be ± 10.0 % of line fit at baseline for samples >0.105 ng/mL. For individual samples ≤ 0.105 ng/mL, a ± 125% of the expected SD (0.0084 ng/mL) specification will be applied (0.0105 ng/mL).

◊ All replicates must be ± 3 SD (± 24%) of the baseline mean dose for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, all replicates must be ± 0.0252 (3 SD) of the baseline mean dose.

To address the concerns of the Agency, BEC has re-calculated these stability results, by sample, using individual replicates. In addition, the low sample results (QCPT1) are presented below without the scaling included in the originally submitted data. The same criteria (± 10.0 % or ± 0.0105 ng/mL depending on sample concentration) was applied to individual samples as was applied to the mean of all samples, ensuring acceptable stability was achieved at each target concentration and that there was not an underlying stability issue being masked by the previous analysis approach. Using a 3 SD criterion for individual replicates gives a probability of 0.0027 that any given replicate during the study would be outside the study; given the sample size in the study (N = 270), no more than 1 replicate would be expected to be outside this specification. The charts below demonstrate that no individual replicates were outside of the 3 SD range.

BEC did not have pre-defined acceptance criteria for imprecision for stability studies. However, based on the individual sample plots Figure 18-8, Figure 18-9, Figure 18-10, and Figure 18-11) no imprecision degradation was observed over time. Additionally, all individual replicates met the expected 3 SD range.

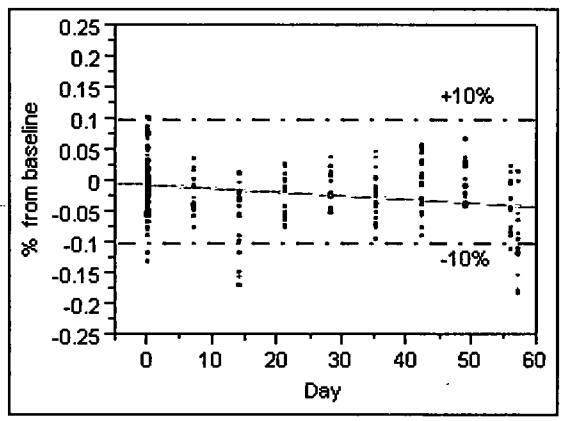
Overall Conclusion: These updated stability analyses support the claim that the AccuTnI+3 stored calibration curve is stable for 56 days.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

The following graphs (Figure 18-7, Figure 18-8, Figure 18-9, Figure 18-10, and Figure 18-11) represent the Stored Calibration Curve stability data using individual sample replicates. The first graph includes the combination of all samples, and the subsequent graphs are for individual samples. The regression lines and standard deviation ranges are noted on each graph.

Figure 18-7: Stored Calibration Curve Stability: Bivariate Fit of % from Baseline, by Day – All Samples and Replicates Combined



Linear Fit: % from baseline = -0.005955 - 0.0006147*Day

Conclusion: When all replicates for all samples are combined, the linear regression meets the ± 10% specification for the stored calibration stability study to 56 days.

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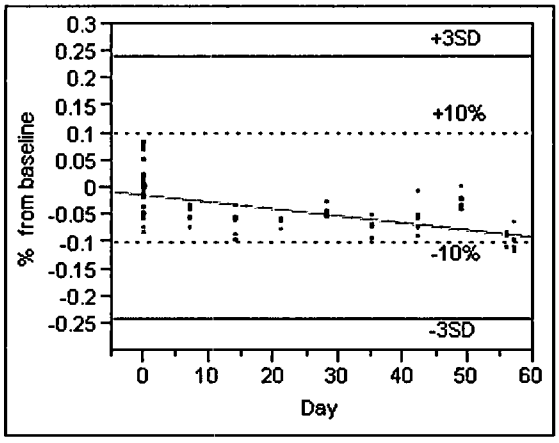
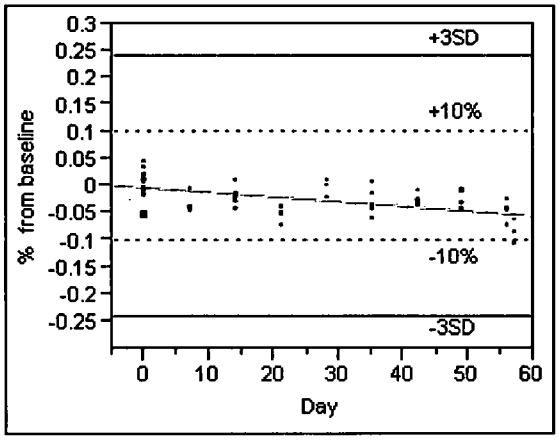
Figure 18-8: Stored Calibration Curve Stability: Bivariate Fit of % from Baseline by Day, Sample Name = Cardiac MORE 2



Linear Fit: % from baseline = -0.013547 - 0.0012478*Day

Conclusion: For the sample Cardiac More 2 (mean dose = 1.00 ng/mL), the linear regression meets the ± 10% criteria for the stored calibration curve stability study to 56 days. Additionally, all individual replicates meet the ± 3 SD criteria.

Figure 18-9: Stored Curve Bivariate Fit of % from Baseline by Day, Sample Name = Cardiac MORE 3



Linear Fit: % from baseline = -0.005182 - 0.0008764*Day

Conclusion: For the sample Cardiac More 3 (mean dose = 14.15 ng/mL), the linear regression meets the ± 10% criteria for the stored calibration curve stability study to 56 days. Additionally, all individual replicates meet the ± 3 SD criteria.

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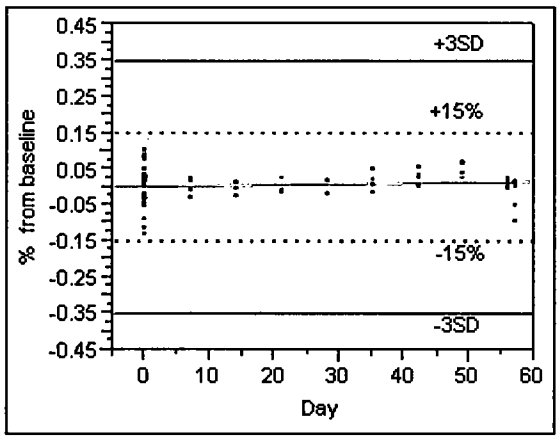
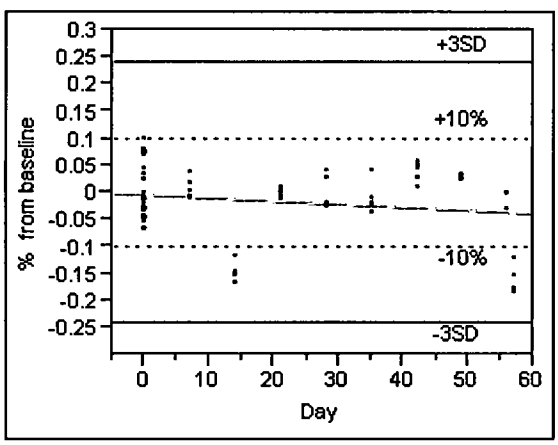
Figure 18-10: Stored Curve Bivariate Fit of % from Baseline by Day, Sample Name = TnI QCPT1



Linear Fit: % from baseline = 0.0018242 + 0.0002012*Day

Conclusion: For the sample QCPT1 (mean dose = 0.071 ng/mL), the linear regression meets the ± 0.0105 ng/mL (± 15% based on concentration) criteria for the stored calibration curve stability study to 56 days. Additionally, all individual replicates meet the ± 3 SD criteria.

Figure 18-11: Stored Curve Bivariate Fit of % from Baseline by Day, Sample Name = TnI QCPT2B



Linear Fit: % from baseline = -0.007127 - 0.000531*Day

Conclusion: For the sample QCPT2B (mean dose = 41.55 ng/mL), the linear regression meets the ± 10% criteria for the stored calibration curve stability study to 56 days. Additionally, all individual replicates meet the ± 3 SD criteria.

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18.d. FDA: Calibrator Real Time Stability: To determine the real time stability of the calibrators, the mean value of each control was calculated and the Z value was calculated as described above in "a". You base your acceptance criteria for controls on the Z value. For normal patient samples, all values must be ≤ 0.04 ng/mL. As discussed above in "a), it seems that normal patient samples should be less than the established 99th percentile of the normal population. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

BEC Response to Question 18.d.

Please refer to our discussion in our response to Question 18.a.i. regarding the description and use of Z-values and the acceptance criteria. The same explanations and criteria presented for Reagent real-time stability apply to Calibrator real-time stability. Calibrator real-time stability results are in Table 18-6, Table 18-7, and Table 18-8 below:

Table 18-6: Calibrator Real-Time Stability Results, Lot 117302

Calibrator Real Time Stability Results, Lot 117302									
Time Point	**Baseline**	**2 Months**	**3 Months**	**4 Months**	**6 Months**	**9 Months**	**12 Months**	**13 Months**	
	Mean (ng/mL)	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	**Mean (ng/mL)**	
Mean Control Values									**Stated Values (ng/mL)**
Control 1	0.055	0.061	0.055	0.055	0.062	0.055	0.055	0.058	0.035-0.079
Control 2	0.744	0.799	0.763	0.731	0.752	0.673	0.760	0.734	0.619-0.855
Control 3	3.678	3.840	3.541	3.474	3.535	3.336	3.378	3.447	2.961-4.088
Control 4	0.021	0.034	0.025	0.023	0.030	0.026	0.021	0.025	0.008-0.052
Control 5	0.958	1.079	1.062	1.013	1.045	0.968	1.048	1.088	0.842-1.163
Control 6	14.379	15.594	15.832	14.951	14.858	14.836	15.348	15.916	12.402-17.127
Control Mean Z Values									**Specification**
Control 1	-0.18	0.39	-0.18	-0.19	0.46	-0.23	-0.16	0.09	±2.00 Z
Control 2	0.12	1.06	0.43	-0.11	0.25	-1.08	0.39	-0.05	±2.00 Z
Control 3	0.55	1.12	0.06	-0.18	0.04	-0.67	-0.52	-0.27	±2.00 Z
Control 4	-0.85	0.39	-0.48	-0.67	0.03	-0.35	-0.83	-0.46	±2.00 Z
Control 5	-0.56	0.94	0.73	0.12	0.52	-0.44	0.56	1.06	±2.00 Z
Control 6	-0.33	0.70	0.90	0.16	0.08	0.06	0.49	0.98	±2.00 Z
Overall Mean Z	-0.21	0.77	0.25	-0.14	0.23	-0.45	-0.01	0.22	±2.00 Z
Z from Baseline		0.98	0.46	0.07	0.44	-0.24	0.20	0.43	±1.00 Z
Individual Assay Normal Patient Results									
Patient 0	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	All results ≤0.02 ng/mL
Patient 1	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Reference Calibrator Mean Dose									
Ref S1	0.311	0.316	0.312	0.297	0.327	0.304	0.319	0.315	
Ref S2	1.21	1.235	1.231	1.226	1.252	1.215	1.222	1.238	
Ref S3	5.01	5.17	5.2	5.14	5.25	5.12	5.17	5.07	
Ref S4	24	24.6	25	24.4	25.4	25.7	25.7	25.1	
Reference Calibrator % Difference from Baseline									
Ref S1		2	0	-5	5	-2	3	1	±11%
Ref S2		2	2	1	3	0	1	2	±11%
Ref S3		3	4	3	5	2	3	1	±10%
Ref S4		3	4	2	6	7	7	5	±10%
Pass/Fail		Pass	Pass	Pass	Pass	Pass	Pass	Pass	

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Table 18-7: Calibrator Real-Time Stability Results, Lot 119776

Calibrator Real Time Stability Results, Lot 119776

Time Point	Baseline	2 Months	4 Months	6 Months	9 Months	12 Months	13 Months	[redacted]
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	[redacted]
Mean Control Values								**Stated Values (ng/mL)**
Control 1	0.055	0.055	0.061	0.057	0.057	0.059	0.056	0.035-0.079
Control 2	0.723	0.719	0.755	0.738	0.680	0.763	0.713	0.619-0.855
Control 3	3.524	3.41	3.568	3.520	3.239	3.600	3.389	2.961-4.088
Control 4	0.033	0.016	0.029	0.027	0.028	0.027	0.029	0.008-0.052
Control 5	1.054	0.999	1.036	1.059	0.966	1.109	1.094	0.842-1.163
Control 6	14.731	14.765	14.531	14.426	13.822	15.878	15.196	12.402-17.127
Control Mean Z Values								**Specification**
Control 1	-0.19	-0.16	0.36	0.01	0.01	0.15	-0.08	±2.00 Z
Control 2	-0.24	-0.30	0.30	0.01	-0.97	0.44	-0.40	±2.00 Z
Control 3	0.00	-0.40	0.16	-0.01	-1.01	0.27	-0.48	±2.00 Z
Control 4	0.32	-1.27	-0.06	-0.24	-0.21	-0.29	-0.10	±2.00 Z
Control 5	0.64	-0.05	0.41	0.70	-0.46	1.32	1.14	±2.00 Z
Control 6	-0.03	0.00	-0.20	-0.29	-0.80	0.94	0.37	±2.00 Z
Overall Mean Z	0.08	-0.37	0.16	0.03	-0.57	0.47	0.08	±2.00 Z
Z from Baseline	[redacted]	-0.45	0.08	-0.05	-0.65	0.39	0.00	±1.00 Z
Individual Assay Normal Patient Results								[redacted]
Patient 0	Pass	Pass	Pass	Pass	Pass	Pass	Pass	All results ≤0.02 ng/mL
Patient 1	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
[redacted]								[redacted]
Reference Calibrator Mean Dose								[redacted]
Ref S1	0.317	0.319	0.324	0.325	0.331	0.324	0.327	[redacted]
Ref S2	1.201	1.229	1.202	1.238	1.249	1.245	1.259	[redacted]
Ref S3	5.00	5.10	5.05	5.03	5.20	5.19	5.12	[redacted]
Ref S4	23.6	24.0	24.4	24.4	24.4	25.2	24.8	[redacted]
Reference Calibrator % Difference from Baseline								[redacted]
Ref S1	[redacted]	1	2	3	4	2	3	±11%
Ref S2	[redacted]	2	0	3	4	4	5	±11%
Ref S3	[redacted]	2	1	1	4	4	2	±10%
Ref S4	[redacted]	2	3	3	3	7	5	±10%
Pass/Fail	[redacted]	Pass	Pass	Pass	Pass	Pass	Pass	[redacted]

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Table 18-8: Calibrator Real-Time Stability Results, Lot 117455

Calibrator Real Time Stability Results, Lot 117455									
Time Point	Baseline	2 Months	3 Months	4 Months	6 Months	9 Months	12 Months	13 Months	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values									**Stated Values (ng/mL)**
Control 1	0.051	0.055	0.053	0.060	0.059	0.053	0.053	0.057	0.035-0.079
Control 2	0.718	0.773	0.757	0.719	0.735	0.686	0.751	0.752	0.619-0.855
Control 3	3.509	3.744	3.673	3.446	3.342	3.274	3.391	3.588	2.961-4.088
Control 4	0.018	0.025	0.014	0.028	0.026	0.024	0.019	0.024	0.008-0.052
Control 5	0.927	1.058	1.056	0.978	1.017	0.966	1.039	1.105	0.842-1.163
Control 6	13.997	15.543	15.420	14.677	14.896	14.306	15.573	16.500	12.402-17.127
Control Mean Z Values									**Specification**
Control 1	-0.51	-0.22	-0.39	0.24	0.16	-0.38	-0.34	-0.08	±2.00 Z
Control 2	-0.33	0.61	0.34	-0.3	-0.03	-0.86	0.24	0.01	±2.00 Z
Control 3	-0.05	0.78	0.53	-0.28	-0.64	-0.89	-0.47	-0.34	±2.00 Z
Control 4	-1.06	-0.44	-1.41	-0.15	-0.35	-0.57	-1.02	-0.60	±2.00 Z
Control 5	-0.95	0.69	0.66	-0.31	0.17	-0.46	0.45	0.77	±2.00 Z
Control 6	-0.65	0.66	0.56	-0.07	0.11	-0.39	0.69	0.93	±2.00 Z
Overall Mean Z	-0.59	0.35	0.05	-0.14	-0.1	-0.59	-0.08	0.12	±2.00 Z
Z from Baseline		0.94	0.64	0.45	0.49	0.00	0.51	0.71	±1.00 Z
Individual Assay Normal Patient Results									
Patient 0	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	All results ≤0.02 ng/mL
Patient 1	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	
[redacted]									
Reference Calibrator Mean Dose									[redacted]
Ref S1	0.311	0.318	0.305	0.311	0.314	0.322	0.312	0.317	[redacted]
Ref S2	1.195	1.243	1.191	1.184	1.215	1.238	1.214	1.250	[redacted]
Ref S3	4.98	5.21	4.97	5.03	5.04	5.19	5.21	5.22	[redacted]
Ref S4	24.0	25.2	24.5	24.6	24.5	25.3	26.1	25.4	[redacted]
Reference Calibrator % Difference from Baseline									
Ref S1	[redacted]	2	-2	0	1	4	0	2	±11%
Ref S2	[redacted]	4	0	-1	2	4	2	5	±11%
Ref S3	[redacted]	4	0	1	1	4	5	5	±10%
Ref S4	[redacted]	5	2	3	2	5	9	6	±10%
Pass/Fail	[redacted]	Pass	Pass	Pass	Pass	Pass	Pass	Pass	[redacted]

As noted in our response to Question 18.a.i., in addition to our standard analysis of the real-time stability data, Beckman Coulter performed additional analysis of the data to address the Agency's concerns that the analysis was assessed on the means of replicates and not on individual replicates.

In establishing the acceptance criteria for individual control sample replicates at each time point, the total

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replicates achieved across the study were considered. Given three standard deviation (3 SD) acceptance interval for individual replicates, the expected probability of having a replicate outside this interval is 0.0027. Using the total number of replicates in the real-time stability protocols (3895 total individual replicates), we have established an expected incidence rate of ≤ 10 replicates outside of the acceptance interval given a normal distribution of data (3895 total replicates * 0.0027 interval of 3 SD = 10.52 replicate incidence rate).

Results of individual replicate evaluation are presented in Table 18-9 below. Graphs of individual controls with all replicates are provided in Appendix 8.

Table 18-9: Results of Individual Replicate Evaluation

	Lot	Replicates Outside Interval	Acceptance Criteria	
Calibrator	117302	1	[redacted]	
	117455	0		
	119776	0		
Total Replicates Outside Interval		1	≤10	PASS

Conclusion:

The analysis of individual controls provides the same conclusions as our original evaluation of the replicate means, in that the data generated supports a 12 month shelf life for the AccuTnI+3 calibrators.

18.e. FDA: Calibrator Open Vial Stability: For the calibrator open vial stability, you propose to scale samples with doses ≤ 0.105 ng/mL to ± 125% of the expected SD and plot the mean doses of all controls versus time compared to baseline values. The best fit linear equation will be calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. Please refer to item 18ai and 18ii above for our recommendations for your stability studies.

BEC Response to Question 18.e.

Open vial calibrator stability results were presented based on samples means in compliance with EP25-A. At the time of the submission, this study was on-going and data was only presented out to eight days. Since that time, the study has been completed out to 63 days (> 60 days) and this full dataset is now provided below. The predetermined acceptance criteria for this study were:

Best fit line through all controls and time points at maximum time point (≥ 60 days) must be ± 10.0 % of line fit at baseline for samples >0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ± 125% of the expected SD (0.0084 ng/mL) specification will be applied.

The 10% specification was developed as follows: A Monte Carlo study, assuming 5% difference is acceptable and an expected imprecision of 8%, provided an additional 5% variability of a regression estimate such that a percent difference specification of ±10% gives 5% type I error. This ratio of specification to imprecision (10%/8% = 125%) was carried over to the difference specification for low

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concentration samples.

Based on the recommendation of the Agency, additional study criteria were developed for evaluating individual sample regressions, and individual replicates:

Best fit line through all replicates of individual controls at maximum time point (≥ 35 days) must be ± 10.0% of line fit at baseline for samples >0.105 ng/mL. For individual samples ≤ 0.105 ng/mL, a ± 125% of the expected SD (0.0084 ng/mL) specification will be applied (0.0105 ng/mL).

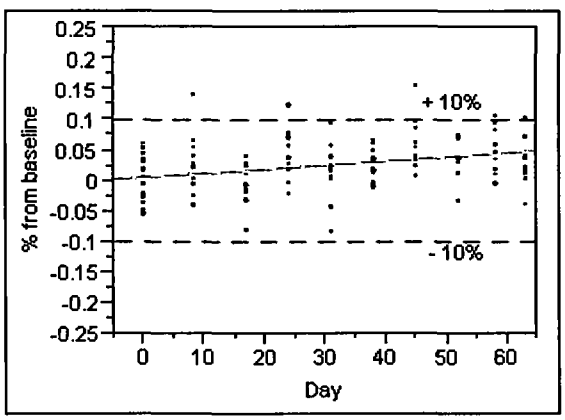
All replicates must be ± 3 SD (± 24.0 %) of the baseline mean dose for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, all replicates must be ± 3 SD (± 0.0252) of the baseline mean dose.

To address the concerns of the Agency, BEC has re-calculated these stability results, by individual sample, using individual replicates. In addition, the low sample results (BioRad1) are presented below without the scaling included in the originally submitted data. The same criteria (± 10.0 % or ±0.0105 ng/mL depending on sample concentration) was applied to individual samples as was applied to the mean of all samples, ensuring acceptable stability was achieved at each target concentration and that there was not an underlying stability issue being masked by the previous analysis approach. Using a 3 SD criteria for individual replicates gives a probability of 0.0027 that any given replicate during the study would be outside the study; given the sample size in the study (N = 132), no replicates should be outside this specification. The charts below demonstrate that no individual replicates were outside of the 3 SD range.

BEC did not have pre-defined acceptance criteria for imprecision for stability studies. However, based on the individual sample plots (Figure 18-13, Figure 18-14, Figure 18-15, and Figure 18-16) no imprecision degradation was observed over time. Additionally, all individual replicates met the expected 3 SD range.

Overall Conclusion: These updated stability analyses support the claim that the AccuTnI+3 calibrator is stable in an open vial for 60 days.

Figure 18-12: Bivariate Fit of % from baseline By Day – All Replicates and Samples Combined



Linear Fit: % from baseline = 0.0050846 + 0.0006749*Day

Conclusion: When all replicates for all samples are combined, the linear regression meets the ± 10% specification for the calibrator open vial study to 60 days.

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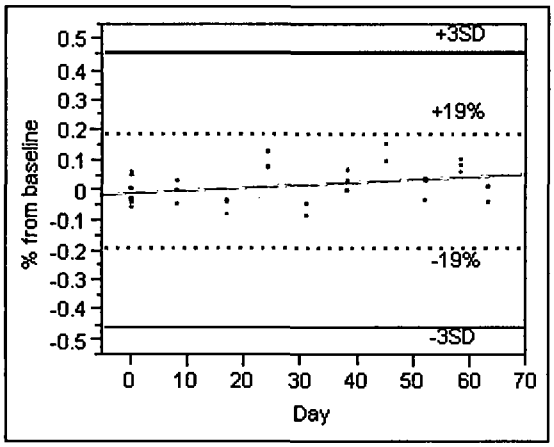
Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

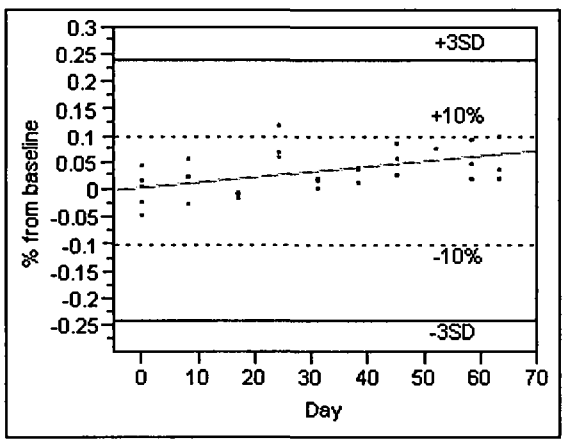
Figure 18-13: Bivariate Fit of % from Baseline by Day Sample Name = BioRad 1



Linear Fit: % from baseline = -0.005801 + 0.0008542*Day

Conclusion: For the sample BioRad 1 (mean dose = 0.055 ng/mL), the linear regression meets the ± 0.0105 ng/mL (± 19% based on concentration) criteria calibrator open vial study to 60 days. Additionally, all individual replicates meet the ± 3 SD criteria.

Figure 18-14: Bivariate Fit of % from Baseline by Day Sample Name = BioRad 2



Linear Fit: % from baseline = 0.003772 + 0.0009814*Day

Conclusion: For the sample BioRad 2 (mean dose = 0.575 ng/mL), the linear regression meets the 10% criteria for calibrator open vial study to 60 days. Additionally, all individual replicates meet the ± 3 SD criteria.

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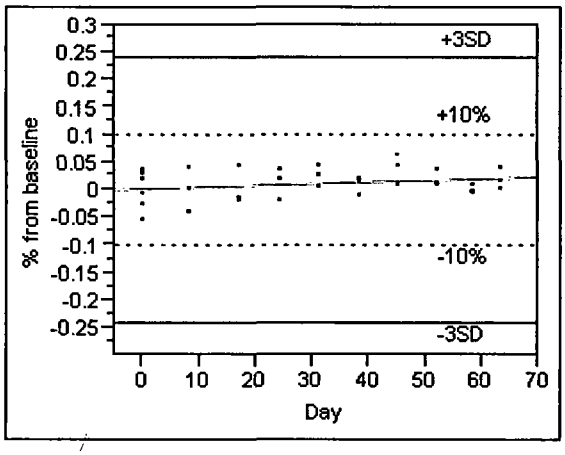
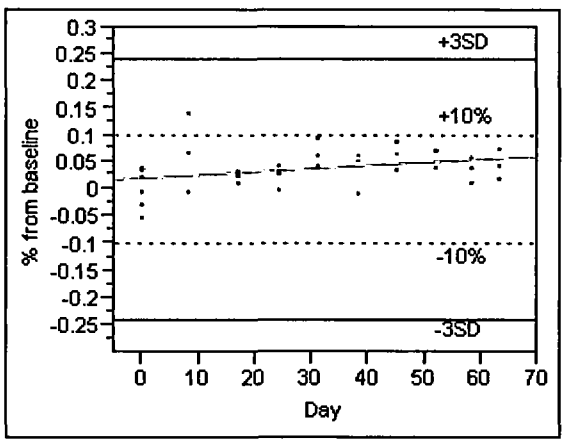
Figure 18-15: Bivariate Fit of % from Baseline by Day Sample Name = BioRad 3



Linear Fit: % from baseline = 0.0024066 + 0.0003095*Day

Conclusion: For the sample BioRad 3 (mean dose = 1.831 ng/mL), the linear regression meets the ± 10% criteria for calibrator open vial study to 60 days. Additionally, all individual replicates meet the ± 3 SD criteria.

Figure 18-16: Bivariate Fit of % from Baseline by Day Sample Name = MORE 3



Linear Fit: % from baseline = 0.0199604 + 0.0005546*Day

Conclusion: For the sample MORE 3 (mean dose = 12.887 ng/mL), the linear regression meets the ± 10% SD criteria for calibrator open vial study to 60 days. Additionally, all individual replicates meet the ± 3 SD criteria.

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Question 19: Device Calibrators:

FDA: It seems that the calibrators for use with the device may not have been previously cleared. They may be cleared with this submission. If this is the case, according to our guidance document on calibrators found at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092801.pdf, you should provide a complete and detailed description of the protocol and procedures for the value assignment process and the validation process for the calibrators (see Section IV b-e of the guidance on calibrators referenced above). Furthermore, please specify what controls and calibrators were used during the value assignment procedure. Please describe how the assigned values were verified to be accurate. Independent controls should be included with each value determination run in order to validate the results. Please also describe the traceability of your calibrators.

BEC Response to Question 19.

The specific information requested above for the AccuTnI+3 Calibrators is referenced below:

- ◊ Information to support calibrator clearance is provided in Appendix 11, in accordance with the Abbreviated 510(k) guidance document.
- ◊ A complete and detailed description of the protocol and procedures for the value assignment process, including a description of its validation, controls and calibrators used in the value assignment procedure, how the calibrator values were accurately assigned, and a description of the independent controls that were used with each calibrator value determination is contained in Section IV.b., "Calibrator Preparation, Value Assignment and Validation," in Appendix 11.
- ◊ Traceability of the AccuTnI+3 Calibrators is described in Section IV.d., "Calibrator Standardization," in Appendix 11.
- ◊ Calibrator draft labeling is presented in Section III., "Labeling," in Appendix 11.
- ◊ Calibrator stability is discussed in BEC's response to Question 18 (Stability studies).

The AccuTnI+3 Calibrator Abbreviated 510(k) has met the requirements of the FDA Guidance, "Abbreviated 510(k) Submission for In Vitro Diagnostic Calibrators."

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Question 20: Labeling:

FDA: In addition to the labeling changes requested in the items above, please address the following. Please send updated labeling with your response.

20.a. FDA: Clinical Sensitivity and Specificity: Please remove all data obtained using cut-offs that were not pre-specified. You should only provide clinical performance data for your pre-specified cut-offs (e.g., 0.02 and 0.03). You should also include the PPV and NPV of your assay at the different time points and at the different hours after symptoms onset in the labeling.

BEC Response to Question 20.a.

Clinical sensitivity and specificity data for any cut-off that was not pre-specified have been removed from the Instructions for Use (IFU).

Sensitivity and specificity data, as well as the positive predictive value (PPV) and negative predictive value (NPV) data at the different time points are included in the IFU only for AccuTnI+3 cut-offs of 0.02 ng/mL and 0.03 ng/mL. The time points included for these parameters are < 8 hours from symptom onset, ≥ 8 hours from symptom onset, baseline (initial collection upon admission to the emergency department), 1 to 3 hours from baseline, and 3-6 hours from baseline.

Please see the revised IFU, provided in Appendix 9.

20.b. FDA: Please remove the information about Risk Stratification for NSTEMI/UA Patients. Please refer to 19a [2a] for additional discussion.

20.c. FDA: We recommend that you remove the "method comparison" information from the labeling. As discussed in the points to consider for Troponin 510(k) submissions provided to you under pre-IDE I100255, a method comparison study that evaluates your test compared to predicate device is not necessary. It is also not necessary to use the predicate device in your clinical study. We will review the cleared clinical performance of your predicate device to your clinical performance to determine whether your device is substantially equivalent. We are also concerned that the method comparison data is not clinically useful.

BEC Response to Questions 20.b. and 20.c.

As noted previously in our response to Question 2 (Intended Use), we have removed all references to "risk stratification" claims for NSTEMI/UA patients from the intended use statement and from the IFU. In addition, the section of the IFU describing method comparison to a predicate device has been removed.

Other changes to device labeling:

- ◊ BEC's analytical performance data and analysis, involving interfering substances and assay cross-reactivity, have been updated to include information from additional testing performed at FDA's request after the Submission, and the device labeling has been revised accordingly.
- ◊ Please also note that low molecular weight heparin (LMWH) remains in the list of interfering substances tested because this molecule is not used to prevent clotting of patient plasma samples, but, rather, is used as a pharmaceutical anti-clotting therapy. It is very common for patients undergoing LMWH therapy to have troponin testing ordered. However, we have removed *sodium heparin* (previously listed as "Heparin-Sodium") from the list of interfering substances to eliminate any confusion on the part of the end users between drug therapy and anticoagulant uses for heparin.
- ◊ And finally, as noted earlier in our response to Question 2 (Intended Use), both serum and plasma

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

	(lithium heparin) remain as preferred sample types in the intended use statement and in the IFU.
◊	The product name has been changed to AccuTnI+3 throughout the device labeling, and provided in Appendix 9 and Appendix 10.

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Question 21: 510(k) Summary

FDA: Please submit a new 510(k) summary with your response.

BEC Response to Question 21.

The new 510(k) Summary and Indications for Use form are provided in Appendix 12.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendices

Appendix 1: Concordance Root Cause Investigation Report

Appendix 2: FDA Meeting Briefing Package

Appendix 3: FDA Response to k121214 Briefing Package

Appendix 4: FDA Teleconference Correspondence

Appendix 5: Emails referred to in the Response to Question 4, Clinical matrix comparison study

Appendix 6: Linearity Results, including higher order fitted estimates, linearity plots, and difference tables referenced in the response to Question 6.c.

Appendix 7: Reagent Pack Real Time Stability Results for individual controls with all replicates as referenced in the response to Question 18.a.

Appendix 8: Calibrator Real Time Stability Results for individual controls with all replicates as referenced in the response to Question 18.a.

Appendix 9: Instructions for Use

Appendix 10: Device Labeling

Appendix 11: Abbreviated 510(k) for AccuTnI+3 Calibrators

Appendix 12: 510(k) Summary and Indications for Use

Appendix 13: References

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 1: Concordance Root Cause Investigation Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 2: FDA Meeting Briefing Package

The following is correspondence BEC sent to the Agency as pre-read material prior to the face-to-face meeting held on October 26, 2012.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

October 17, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
ATTN: Paula Velasco Caposino, Ph.D

SUBJECT: **K121214 Meeting Briefing Package**

Access AccuTnI on the Access 2 Immunoassay Systems

Dear Dr. Caposino,

Thank you for meeting with us via teleconference Thursday, October 4, 2012, to discuss Beckman Coulter's ("BEC") 510(k) submission for AccuTnI on the Access 2 Immunoassay Systems, 510(k) K121214, and agreeing to have a face-to-face meeting on October 26, 2012. We are providing this briefing package to help ensure a productive meeting.

The briefing package provides an update on the results of our investigation of anomalous data seen in our Thermal Sensitivity – Impact on Low Dose Concordance/Agreement study ("concordance") as well as information related to certain issues raised in the Agency's June 20, 2012 deficiency letter that BEC would like to discuss. These issues include:

- Thermal Sensitivity – Acceptance Criteria
- Calibration
- Temperature Set Points Specifications
- Natural, Unmodified Patient Sample Rationale
- Sample Matrix comparison

If you have any questions or requests for additional information, please feel free to contact me at (612) 804-1728 at your convenience.

Sincerely,

Scott Cundy, RAC
VP Quality and Regulatory Affairs

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Introduction

After evaluating the Division's concerns and questions in the 510(k) deficiency letter ("Letter"), we realize now that we should have provided the Division with more detailed information about the rationales behind some of our study designs. Therefore, we are providing additional background on the testing schema strategies, acceptance criteria, and the specific assay and sample characteristics that led to the design of our analytical studies. Also, in light of concerns the Division has raised regarding concordance results in a BEC analytical study that was part of the 510(k) submission, BEC felt it was important to provide background on the work we have done since receiving the letter to investigate this issue. Additionally, BEC would like to have a technical discussion and share our strategy for addressing a few questions that were called out in the deficiency letter.

The specific questions are related to:

- Thermal Sensitivity – Acceptance Criteria
- Calibration
- Temperature Set Points
- Patient Sample Rationale
- Sample Matrix comparison

The following information will lay the groundwork for our upcoming technical discussion.

Thermal Sensitivity – Impact on Low Dose Concordance/Agreement (Concordance)

Division Comment: In its Letter, the Division stated *"...We performed further analysis using Passing-Bablok regression. The estimates of the intercepts in these regression was always 0, but, for example, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 with a 95% confidence interval of (1.36, 1.54) and for measurements taken in 18 and 26°C the slope was 1.33 with a 95% confidence interval of (1.26, 1.40). Based on this analysis and the analysis provided in the table above, we have serious concerns that higher temperatures consistently yielded higher troponin measurements. Therefore, we do not believe that the data provided demonstrates concordance across temperatures."*

BEC Clarifying Points:

BEC agrees that the temperature concordance verification study exhibited higher than expected thermal bias after correction by the thermal algorithm. Based on BEC's further evaluations it has been determined that this bias was the result of a subset of patient samples exhibiting anomalous thermal response in the concordance study.

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Upon receipt of the Letter, BEC launched an immediate investigation to identify the root cause of this anomalous behavior. A full review of our historical development and verification data showed that this magnitude of thermal bias had not been observed previously. We systematically evaluated the probable causes of this bias and were able to rule out: (1) instrument; (2) calibrator lot; (3) reagent lot; (4) software; (5) thermal correction algorithm; (6) thermal chamber issues; (7) study date; (8) operator; (9) run order; (10) sample shipment; and (11) analyte concentration. Further investigation focused on three areas.

1. Sample acquisition, handling, storage, and processing
2. Thermal properties of Troponin I, its isoforms and degradation products
3. Additional data analysis and retest

Details on the testing and analyses are described below.

1. Sample acquisition, handling, storage, and processing

All samples used in the analytical concordance study were de-identified residual patient samples acquired from external vendors. As such, acquiring additional volumes from those specific patients for our investigation and further testing was not possible. Based on our review we determined that one particular vendor provided the majority of samples used in the concordance study that exhibited the observed thermal bias.

BEC investigated the collection, storage and shipping processes used by this vendor to collect the samples, and learned that the samples had been stored at 4°C for approximately 2-6 weeks before they were frozen and shipped to BEC. This sample handling deviates from the specimen collection and preparation guidelines in AccuTnI's Instructions for Use ("IFU").

BEC could not reproduce the anomalous thermal response with samples that were collected under IFU conditions and then subjected to up to 5 additional freeze/thaw cycles or extended storage up to 6 weeks at 4°C. Other vendor handling and/or storage parameters could not be simulated, therefore we continued with our investigation as described below.

2. Thermal properties of Troponin I ("TnI"), its isoforms and degradation products

Because the instability of the TnI molecule has been well documented in the literature, BEC also investigated the potential impact of molecular and structural properties of TnI on the resultant thermal response. A model system was created using a native troponin I-C complex spiked into plasma and serum samples at various concentrations. Size exclusion chromatography and subsequent immunoassay analysis revealed formation of high molecular weight TnI aggregates during extended storage (up to 6 weeks) at 4°C. This phenomenon was sample specific, and resulted in altered thermal response. In addition, multiple TnI isoforms have been tested. Extended storage of certain model system samples and TnI isoforms also demonstrated altered

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thermal response. This observation corroborates the hypothesis that sample handling is a probable root cause.

3. *Additional Data Analysis and Retest*

BEC reanalyzed historical data sets with the Passing-Bablok ("P-B") regression method used by the Division. One data set was from a concordance study conducted during our development phase, with a design comparable to that of the submitted concordance study and samples in the range of 0 to 0.4 ng/mL. The P-B regression slope results are listed in Table 1 and demonstrated expected thermal performance:

Table 1: Development phase concordance study

Study Date	N	Temperature	P-B Slope
Sept, 2011	100	18°C vs. 26°C	1.08
	100	20°C vs. 28°C	1.00

In the original 510(k) submission, BEC conducted a method comparison study that analyzed samples over the entire dose range using P-B regression. Subsequently, BEC analyzed only the low-dose samples of the method comparison study (doses between 0 and 0.4 ng/mL, similar to the concordance study range) using the P-B regression method. BEC was able to confirm that these samples were collected and handled per our IFU specimen handling conditions. These P-B regression slope results are listed in Table 2, and again, demonstrated expected thermal performance:

Table 2: Verification phase Low-Dose range analysis of method comparison study

Study Date	N	Temperature	P-B Slope
Mar, 2012	48	18°C vs. 28°C	1.02

Lastly, we conducted a new, prospective collection in which samples were handled per our IFU specimen handling conditions. We then used these samples to repeat the entire concordance study. The P-B regression slope results are listed in Table 3 and demonstrated expected thermal performance consistent with the results shown in Tables 1 and 2:

Table 3: Repeated Concordance study with newly acquired samples

Study Date	N	Temperature	P-B Slope
Oct, 2012	109	18°C vs. 26°C	0.96
	110	20°C vs. 28°C	0.98

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In conclusion, both our historical data and the newly conducted concordance study, with samples handled per the IFU, demonstrate the effectiveness of the thermal algorithm, and that the submitted concordance data is not representative of the typical sample thermal behavior. The data above supports our hypothesis that the anomalous results were isolated to the single sample set used for the submitted concordance study. We will submit the results of the new "Thermal Sensitivity: Impact on Low-Dose Concordance" study with our deficiency response.

Thermal Sensitivity- Acceptance Criteria

Division Comment: In its Letter, the Division stated, "*... we do not understand the rationale of your acceptance criteria. Therefore, we are concerned that this study design does not demonstrate that the thermal sensitivity issue has been resolved.*"

The Division raised this issue in Sections 1ai, 1b, 1c, 6b, 7ai, and 7bii of the Letter.

BEC Clarifying Points:

A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

- The acceptance criterion of "average slope ≤ 0.010" cited in the thermal robustness study corresponds to a change in concentration of ≤1% per degree C. For the entirety of the assay's ambient operating temperature range, this translates to a maximum 10% allowable bias due to temperature changes.
- The acceptance criterion is consistent with the method comparison accuracy acceptance criteria of ≤10% for the AccuTnI assay; that is, a slope of 1.00 ± 0.010 is equivalent to a 10% thermal bias over the entire operating range.
- This specification is consistent with allowable bias goals cited by multiple sources such as Rilibak, Ricos, Royal College of Pathologists of Australasia Analytical Quality Requirements, etc.

Calibration

Division Comment: In several sections of its Letter, Division stated, "*We do not know how to interpret this study since it was not performed as this device is intended to be used. While you claim that the instrument calibration is stable for 56 days (irrespective of ambient temperature), this study was performed by generating a calibration curve at each temperature tested. We are concerned that the test results obtained may be more accurate if measurement is taken at the same temperature it was calibrated.*"

The Division raised this issue in Sections 1b, 1c, 5a, 5b, 5c, and 10 of the Letter.

BEC Clarifying Points:

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these three temperatures. Table 4 below shows P-B slope results and Pearson correlation coefficients for nine different calibration/sample temperature combinations.

Table 4: Impact of calibration temperature on accuracy of results

Calibration Temperature °C	Sample Run Temperatures °C	P-B Slope	Pearson r-value	n
18	18v23	0.99	1.00	108
	18v28	0.97	1.00	108
	23v28	0.97	1.00	108
23	18v23	1.02	1.00	108
	18v28	0.98	1.00	108
	23v28	0.96	1.00	108
28	18v23	1.01	1.00	108
	18v28	1.00	1.00	108
	23v28	0.99	1.00	108

- Specific to Division questions 5a (LoB), 5b (LoD), and 5c (LoQ), per CLSI guideline EP17-A2, in order to establish performance characteristics the manufacturer must include multiple variables (e.g. multiple reagent lots, multiple instruments, multiple days, multiple calibrations, large numbers of replicates, etc.). These variables were incorporated into our study design as described within our pre-IDE. The requirements of EP17-A2 preclude data reduction from a single calibration curve.
- BEC conducted our studies in accordance with the AccuTnI Instructions for Use, to the extent permitted by the complexity of the studies and the requirements of the CLSI guidelines. Specific to the calibration questions, BEC does not plan to conduct additional studies for Thermal Sensitivity-robustness; Thermal Sensitivity- impact on cross-temperature method comparison; LoB, LoD, LoQ, and precision based upon the above rationale.

Temperature Set Point Specifications

Division Comment: In its Letter, Division stated, *"We are concerned that the criteria of ±2 °C for your temperature studies may be too broad for your thermal sensitivity studies."*

The Division raised this issue in Sections 1d, 5e, 6d, 8g, 9, 10, and 12 of the Letter.

BEC Clarifying Points:

A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

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- To conduct the required multiple temperature studies, BEC installed several thermally controlled environmental rooms and chambers. The capability of these facilities range from +/- 1C to +/-2C depending on the size, HVAC system and load.
- During study execution, actual temperatures were monitored, recorded and verified to be within ±2°C of the set point. Further data analysis determined that ~80% of the recorded temperatures were within ±1°C of the set point. This ±2°C range allowed BEC to perform studies in an environment that is representative of clinical laboratory ambient temperature variability.
- Studies incorporated testing across the operating range of 18-28°C. In addition, in Section 8.12 of the submission, the study titled Thermal Sensitivity-Robustness, included temperature set-points beyond the operating range, at 16°C ±1°C and 30°C ±1°C, assuring algorithm effectiveness up to and beyond the recommended temperature range of 18-28°C.
- BEC will provide Division the recorded actual ambient temperatures for existing thermal studies to demonstrate that the system was challenged with the appropriate rigor across the full operating temperature range (18-28°C) and the ±2 °C requirement for proper operation of the thermal chambers is appropriate.

Natural, Unmodified Patient Sample Rationales

In its Letter, the Division stated, *"...we recommend that you use natural, unmodified patient samples... "*

The Division raised this issue in Sections 5d, 7aii, 7biii, and 10 of the Letter.

BEC Clarifying Points:

A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

- Many of the studies where this theme was identified were conducted over multiple runs, instruments, temperatures, and/or reagent lots. As such, large sample volumes of 20 – 50 mL were required. Therefore, for these studies, pooled or spiked samples were required.
- Individual, natural patient samples containing cTnI analyte are typically available as residual draws in quantities of only 0.5-2 mL, much less than the volume needed for these studies. The conditions of individuals with elevated troponin results preclude collection of substantial volumes of serum or plasma.
- The commercial controls used in the studies are reflective of the thermal response of natural patient samples.
- However, BEC did conduct certain studies with natural patient samples where the required collection volumes could be obtained. For example, the method comparison

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and sample type comparison studies included in the submission were designed and conducted to confirm the accuracy of AccuTnI and algorithm performance using individual, natural, unmodified patient samples.

BEC does not plan to conduct additional studies based on the above.

Sample Matrix comparison

Division Comment: In its Letter, Division stated, "....We still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) when serum samples are used at the pre-specified cut-offs."

The Division raised this issue in Sections 2b and 4 of the Letter.

BEC Clarifying Points:

A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

- BEC contacted the Division in January 2011 to gain additional clarity on the matrix comparison requirements.
- In response to BEC's inquiry, the Division provided the following response: "As indicated in the Points to Consider document from April 2010, we recommend that if you are pursuing more than a single matrix type claim for your device then you should collect and test specimens for each claimed sample matrix, such as whole blood and plasma, to obtain clearance for multiple matrices. If you decide not to include all claimed matrix types in your clinical performance evaluation, then you will need to demonstrate that there is little to no bias between sample types in a matrix comparison study using substantially narrow acceptance criteria. In addition, you will need to include an adequate number of samples around the assay cutoff. The results from your matrix comparison study will be evaluated during the review of your device premarket notification."
- Consistent with the Division's feedback, we did not include all claimed matrix types in our clinical performance evaluation, but instead we demonstrated that there is little to no bias between serum and lithium heparin plasma used in the matrix comparison study. Excellent agreement was shown between the matrices for specimens from the pivotal study as documented in the 510(k) submission (n= 107, slope= 1.00, 95% CI= 0.98 – 1.00, Y intercept= 0.00, r= 1.00) to support the use of serum as a matrix for the AccuTnI assay.
- To provide additional information to further address the Division feedback that we focus on patients near the clinical cut off, additional analysis of the data derived from the target population in the pivotal clinical trial was performed. The range was truncated to include only patients with troponin levels from 0.01 to 0.4 ng/ml. Similar to what was observed in the wider range analysis, excellent agreement between the two matrices

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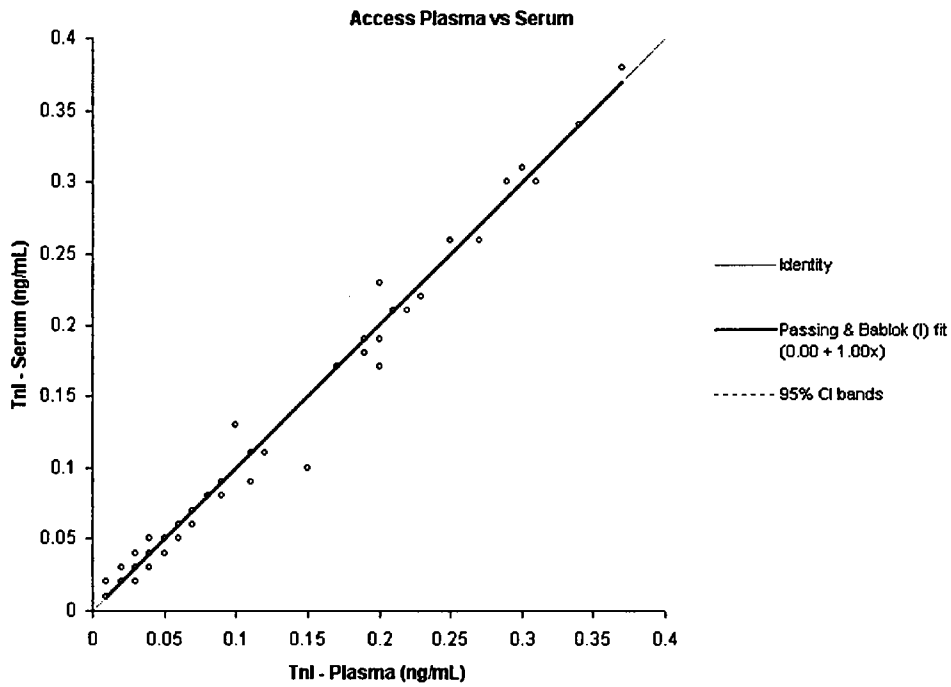
was observed. n= 86, P-B slope= 1.00, P-B intercept= 0.00, Pearson r= 0.99. See Figure 2 below:

Figure 2. Low Concentration Range Serum vs. Plasma Matrix comparison



- In addition, BEC has reviewed the 510(k) Substantial Equivalence Determination Decision Summary for the predicate device, ADVIA Centaur® TnI-Ultra, (k)053020. The linear regression equation for lithium heparin vs. serum is described as follows:

  Centaur: y(Heparinized plasma) = 0.91x(serum) + 0.67; r = 0.964 and n = 53.

  BEC's linear regression equation for lithium heparin vs. serum is described as follows:

  BEC: y(Heparinized plasma) = 1.00x(serum) + 0.00; r = 1.00 and n = 107

- Given the excellent correlation observed between serum and lithium heparin plasma for specimens both near the clinical cut-off and at higher levels tested in accordance with the Division's recommendations, and performance that is substantially equivalent to that described in the Decision Summary by the predicate device, we request that the claimed use of serum be retained in the Intended Use.

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Summary

In our follow-up meeting with the Division's technical reviewers, BEC would like to discuss the additional background information for our study designs presented above, and gain agreement on the path forward with respect to those studies.

Please note that BEC intends to address all other Division concerns as follows.

Division request	BEC planned action
Retest	Retest and provide results for: • Thermal sensitivity: concordance • Linearity • Interfering substances • Cross Reactivity
Modify Labeling (Instructions for Use)	Remove from Instructions for Use: • References to risk stratification • Data obtained from cutoffs not pre-specified • method comparison data to predicate Add to Instructions for Use: • PPV and NPV for additional time points after admission and symptom onset
Clarification and/or additional analysis	Provide clarification and/or additional analysis as requested for: • Modified analyses for stability data • Pivotal clinical trial questions and analyses • Description of the algorithm and its development • Hardware questions • Software questions • Calibrator description, value assignment and traceability

Thank you for your consideration of these topics, and we look forward to the opportunity to further discuss our submission with you.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4) Meeting Presentation

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MEMORANDUM

TO: Scott Cundy
Vice President Quality and Regulatory Affairs
Beckman Coulter, Inc.

FROM: Paula Caposino
Scientific Reviewer
FDA/CDRH/OIR/DCTD

RE: k121214 Meeting Briefing Package
DEVICE: Access AccuTnI on the Access 2 Immunoassay Systems
DATED: October 17, 2012

DATE: November 7, 2012

Dear Scott Cundy:

Thank you for submitting this information for our review. As discussed during the October 26, 2012 meeting, we are providing written feedback to the topics that we did not discuss during our meeting. Please find enclosed our responses based on the current information reviewed. Please note that this is an informal communication that represents the best judgment of the Office of In Vitro Diagnostics and Radiological Health staff and consultants who reviewed your proposal. It does not constitute an advisory opinion and does not bind or otherwise obligate or commit the agency to the views expressed, as per 21 CFR 10.85(k).

FDA responses:

1. **Thermal Sensitivity – Impact on Low Dose Concordance/Agreement (Concordance):**
   FDA note: *This topic was discussed during the October 26, 2012 meeting.*

2. **Thermal Sensitivity- Acceptance Criteria:** In its Letter, the Division stated, "... *we do not understand the rationale of your acceptance criteria. Therefore, we are concerned that this study design does not demonstrate that the thermal sensitivity issue has been resolved.*" The Division raised this issue in Sections 1ai, 1b, 1c, 6b, 7ai, and 7bii of the Letter.

   BEC Clarifying Points: A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points:

   - The acceptance criterion of "average slope ≤ 0.010" cited in the thermal robustness study corresponds to a change in concentration of ≤1% per degree C. For the entirety of the assay's ambient operating temperature range, this translates to a maximum 10% allowable bias due to temperature changes.
   - The acceptance criterion is consistent with the method comparison accuracy acceptance criteria of ≤10% for the AccuTnI assay; that is, a slope of 1.00 ± 0.010 is equivalent to a 10% thermal bias over the entire operating range.

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- This specification is consistent with allowable bias goals cited by multiple sources such as Rilibak, Ricos, Royal College of Pathologists of Australasia Analytical Quality Requirements, etc.

FDA response: *We are concerned that if your studies demonstrate consistent thermal bias, then the thermal sensitivity issue has not been resolved. In your response, you need to demonstrate that the performance of your device is equivalent irrespective of ambient temperature (within the context of the assay's imprecision) and that your device is safe for patient use.*

3. **Calibration:** In several sections of its Letter, Division stated, "*We do not know how to interpret this study since it was not performed as this device is intended to be used. While you claim that the instrument calibration is stable for 56 days (irrespective of ambient temperature), this study was performed by generating a calibration curve at each temperature tested. We are concerned that the test results obtained may be more accurate if measurement is taken at the same temperature it was calibrated.*" The Division raised this issue in Sections 1b, 1c, 5a, 5b, 5c, and 10 of the Letter.

   BEC Clarifying Points: A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

   - AccuTnI patient samples exhibit a "thermal sensitivity" of approximately 3.5% per degree Celsius. However, the calibrator, which uses a recombinant antigen, does not exhibit the same thermal sensitivity. As a result, recalibration does not correct for the temperature induced shift of reported results. See Figure 1.
   - The thermal algorithm was developed to compensate for the difference in thermal response between samples and calibrators.
   - For the 18 °C, Normal Laboratory Conditions (~23 °C), and 28 °C constant-temperature studies, calibration was performed at each respective temperature, to demonstrate that even though the calibrator signals do not change with ambient temperature, the system can perform valid calibrations at the extremes of the temperature range with appropriate software algorithm adjustment of sample results.
   - For the multi-temperature studies, a single calibration was conducted at approximately 23 °C and used to determine results across the entire temperature range, thereby demonstrating the effectiveness of the algorithm across the operating range using a single calibration.
   - Existing method comparison data generated at multiple calibration and run temperatures has been reanalyzed and demonstrates that test results are accurate and meet acceptance criteria, independent of calibration temperature. Calibrations established at 18°C, 23°C, and 28°C were used to correlate patient results generated at these three temperatures. Table 4 below shows P-B slope results and Pearson correlation coefficients for nine different calibration/sample temperature combinations.
   - Specific to Division questions 5a (LoB), 5b (LoD), and 5c (LoQ), per CLSI guideline EP17-A2, in order to establish performance characteristics the manufacturer must include multiple variables (e.g. multiple reagent lots, multiple instruments, multiple days, multiple calibrations, large numbers of replicates, etc.). These variables were

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incorporated into our study design as described within our pre-IDE. The requirements of EP17-A2 preclude data reduction from a single calibration curve.

- BEC conducted our studies in accordance with the AccuTnI Instructions for Use, to the extent permitted by the complexity of the studies and the requirements of the CLSI guidelines. Specific to the calibration questions, BEC does not plan to conduct additional studies for Thermal Sensitivity-robustness; Thermal Sensitivity- impact on cross-temperature method comparison; LoB, LoD, LoQ, and precision based upon the above rationale.

FDA response: *In addition to understanding "that even though the calibrator signals do not change with ambient temperature, the system can perform valid calibrations at the extremes of the temperature range with appropriate software algorithm adjustment of sample results", we need to understand the performance of the device as it is intended to be used. Regarding the limits of detection studies (i.e., LoB, LoD and LoQ) while we encourage different sources of variables in your studies, these should be within the context of the expected variability that the end user would experience. As such, it seems that calibrating at every temperature is not as this device is to be used. Therefore, in your response, please provide data for the requested studies demonstrating the performance of this device as intended for use. As discussed above in item 2, in your response, you need to demonstrate that the performance of your device is equivalent irrespective of ambient temperature and that your device is safe for patient use. Furthermore, where there are differences in the performance with calibration at each temperature compared to calibration at a single temperature, you should investigate the reason for the difference in the performance and provide your findings for FDA review.*

4. **Temperature Set Point Specifications:** In its Letter, Division stated, "*We are concerned that the criteria of ±2 °C for your temperature studies may be too broad for your thermal sensitivity studies.*" The Division raised this issue in Sections 1d, 5e, 6d, 8g, 9, 10, and 12 of the Letter.

   BEC Clarifying Points: A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

   - To conduct the required multiple temperature studies, BEC installed several thermally controlled environmental rooms and chambers. The capability of these facilities range from +/- 1C to +/-2C depending on the size, HVAC system and load.
   - During study execution, actual temperatures were monitored, recorded and verified to be within ±2°C of the set point. Further data analysis determined that ~80% of the recorded temperatures were within ±1°C of the set point. This ±2°C range allowed BEC to perform studies in an environment that is representative of clinical laboratory ambient temperature variability.
   - Studies incorporated testing across the operating range of 18-28°C. In addition, in Section 8.12 of the submission, the study titled Thermal Sensitivity-Robustness, included temperature set-points beyond the operating range, at 16°C ±1°C and 30°C ±1°C, assuring algorithm effectiveness up to and beyond the recommended temperature range of 18-28°C.

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- BEC will provide Division the recorded actual ambient temperatures for existing thermal studies to demonstrate that the system was challenged with the appropriate rigor across the full operating temperature range (18-28°C) and the ±2 °C requirement for proper operation of the thermal chambers is appropriate.

FDA response: *Understood. We will review your complete response and make our determination.*

5. **Natural, Unmodified Patient Sample Rationales:** In its Letter, the Division stated, "*...we recommend that you use natural, unmodified patient samples...* " The Division raised this issue in Sections 5d, 7aii, 7biii, and 10 of the Letter.

   BEC Clarifying Points: A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

   - Many of the studies where this theme was identified were conducted over multiple runs, instruments, temperatures, and/or reagent lots. As such, large sample volumes of 20 – 50 mL were required. Therefore, for these studies, pooled or spiked samples were required.
   - Individual, natural patient samples containing cTnI analyte are typically available as residual draws in quantities of only 0.5-2 mL, much less than the volume needed for these studies. The conditions of individuals with elevated troponin results preclude collection of substantial volumes of serum or plasma.
   - The commercial controls used in the studies are reflective of the thermal response of natural patient samples.
   - However, BEC did conduct certain studies with natural patient samples where the required collection volumes could be obtained. For example, the method comparison and sample type comparison studies included in the submission were designed and conducted to confirm the accuracy of AccuTnI and algorithm performance using individual, natural, unmodified patient samples. BEC does not plan to conduct additional studies based on the above.

   FDA response: *We still recommend that you provide data for all requested studies using natural patient samples (i.e., not spiked with exogenous cTnI analyte). However, we agree that the use of pooled patient samples with relevant cTnI concentrations (that are not spiked with exogenous cTnI analyte) are acceptable for the requested studies (i.e., LoD, LoQ, field effectiveness studies and precision studies).*

6. **Sample Matrix comparison:** In its Letter, Division stated, "....We still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) when serum samples are used at the pre-specified cut-offs." The Division raised this issue in Sections 2b and 4 of the Letter.

   BEC Clarifying Points: A complete response to this issue will be provided in BEC's final response to the deficiency letter. However, for the purposes of facilitating a discussion at our meeting, we wanted to provide some clarification around a few points –

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- BEC contacted the Division in January 2011 to gain additional clarity on the matrix comparison requirements.
- In response to BEC's inquiry, the Division provided the following response: "As indicated in the Points to Consider document from April 2010, we recommend that if you are pursuing more than a single matrix type claim for your device then you should collect and test specimens for each claimed sample matrix, such as whole blood and plasma, to obtain clearance for multiple matrices. If you decide not to include all claimed matrix types in your clinical performance evaluation, then you will need to demonstrate that there is little to no bias between sample types in a matrix comparison study using substantially narrow acceptance criteria. In addition, you will need to include an adequate number of samples around the assay cutoff. The results from your matrix comparison study will be evaluated during the review of your device premarket notification."
- Consistent with the Division's feedback, we did not include all claimed matrix types in our clinical performance evaluation, but instead we demonstrated that there is little to no bias between serum and lithium heparin plasma used in the matrix comparison study. Excellent agreement was shown between the matrices for specimens from the pivotal study as documented in the 510(k) submission (n= 107, slope= 1.00, 95% CI= 0.98 – 1.00, Y intercept= 0.00, r= 1.00) to support the use of serum as a matrix for the AccuTnI assay.
- To provide additional information to further address the Division feedback that we focus on patients near the clinical cut off, additional analysis of the data derived from the target population in the pivotal clinical trial was performed. The range was truncated to include only patients with troponin levels from 0.01 to 0.4 ng/ml. Similar to what was observed in the wider range analysis, excellent agreement between the two matrices was observed. n= 86, P-B slope= 1.00, P-B intercept= 0.00, Pearson r= 0.99. See Figure 2 below:
- In addition, BEC has reviewed the 510(k) Substantial Equivalence Determination Decision Summary for the predicate device, ADVIA Centaur® TnI-Ultra, (k)053020. The linear regression equation for lithium heparin vs. serum is described as follows:

  Centaur: y(Heparinized plasma) = 0.91x(serum) + 0.67; r = 0.964 and n = 53.

  BEC's linear regression equation for lithium heparin vs. serum is described as follows:

  BEC: y(Heparinized plasma) = 1.00x(serum) + 0.00; r = 1.00 and n = 107

- Given the excellent correlation observed between serum and lithium heparin plasma for specimens both near the clinical cut-off and at higher levels tested in accordance with the Division's recommendations, and performance that is substantially equivalent to that described in the Decision Summary by the predicate device, we request that the claimed use of serum be retained in the Intended Use.

FDA response: *I cannot find the record of our interaction with you from January 2011 (it does not seem to be part of the Pre-IDE 1100255). However, since the cut-offs for troponin assays based on the 99th percentile are much lower than the cut-offs of previously cleared assays, the approach used by the predicate device to obtain clearance for several sample types may no longer be appropriate. Specifically, for the predicate device, the diagnostic*

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cut-off was based on the definition of MI as described by the World Health Organization (0.9ng/mL). This cut-off is 30 times higher than your ROC determined cut-off and 45 times higher than your cut-off using the 99th percentile. Therefore, we are not sure if the regression model will reliably predict the clinical performance of another sample type using your new and much lower diagnostic cut-offs. As we have consistently recommended (in the Points to Consider document from April 2010, in your description of our response to your inquiry from January 2011 and in our letter requesting additional information) in order to claim the use of multiple matrices, you should demonstrate the clinical performance of your device using each sample type that you intend to claim.

If you have any questions, please feel free to contact me.

Regards,

Paula V. Caposino

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
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Appendix 4: FDA Teleconference Correspondence

The following is the correspondence sent to the Agency as pre-read material prior to the teleconference held on November 16, 2012.

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November 13, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
ATTN: Paula Velasco Caposino, Ph.D

SUBJECT: Topics for November 16, 2012 Teleconference
Access AccuTnI on the Access 2 Immunoassay Systems, 510(k) K121214

Dear Dr. Caposino,

Thank you for providing your written feedback regarding the subjects that we were not able to discuss during the October 26, 2012 meeting in Washington DC, and for agreeing to meet with us via teleconference to further discuss these topics.

Beckman Coulter would like to seek alignment with the Division in the following areas, which are described in more detail on the following pages:

- Sample Matrix Comparison
- Natural, Unmodified Patient Sample Rationale
- Calibration Strategy

We have addressed FDA's concerns and have provided additional background information below in preparation for our teleconference with the Division on Friday, Nov. 16.

Sincerely,

Scott Cundy, RAC
VP Quality and Regulatory Affairs

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Sample Matrix Comparison

FDA response: *I cannot find the record of our interaction with you from January 2011 (it does not seem to be part of the Pre-IDE I100255). However, since the cut-offs for troponin assays based on the 99th percentile are much lower than the cut-offs of previously cleared assays, the approach used by the predicate device to obtain clearance for several sample types may no longer be appropriate. Specifically, for the predicate device, the diagnostic cut-off was based on the definition of MI as described by the World Health Organization (0.9 ng/mL). This cut-off is 30 times higher than your ROC determined cut-off and 45 times higher than your cut-off using the 99th percentile. Therefore, we are not sure if the regression model will reliably predict the clinical performance of another sample type using your new and much lower diagnostic cut-offs...*

BEC has located and attached the email correspondence (below) between Dr. Kurtis Bray (BEC) and Dr. Ileana Elder (FDA) for your reference.

BEC has also performed additional statistical analyses of the data from the clinical sample matrix comparison study to demonstrate that the assay will reliably predict the clinical performance of both sample types at the established diagnostic cutoffs.

Please review the material provided below. The additional analyses demonstrate the equivalence of serum and plasma matrices, and we will be prepared to discuss any additional questions you have regarding this topic.

In correspondence with FDA, Beckman asked for specific clarification about requirements for validation of additional matrix types. In an e-mail to lead reviewer, Ileana Elder, dated January 13, 2011 we asked:

> From: krbray@beckman.com [mailto:krbray@beckman.com]
> Sent: Thursday, January 13, 2011 10:28 AM
> To: Elder, Ileana
> Subject: I100255
>
> Dear Dr. Elder,
>
> I am writing with a brief question concerning one point of our specimen testing plans for our ongoing prospective AccuTnI clinical trial for the Access and DxI assay systems.
>
> Our current primary specimen type for TnI measurement is lithium heparin, but we also wish to validate the use of serum and include that in our labeling as well. Thus, consistent with the direction provided in FDA's "Points to Consider" document, and using CLSI guidance EP 09 as a guide, our plan is to test the lithium heparin specimens from entire clinical cohort. The use of serum will at the same time be validated per EP 09 by testing and comparing a sufficient subset of serum specimens from the relevant target clinical population enrolled in our clinical trial.

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Please confirm that this approach is aligned with FDA's expectations for validation of multiple specimen types. Thank you.

Kurt Bray

Kurtis R. Bray, Ph.D.
Director of Clinical Research
Beckman Coulter, Inc.
2470 Faraday Avenue
Carlsbad, CA 92010

Dr. Elder replied via e-mail on January 18, 2011:

"Elder, Ileana" <Ileana.Elder@fda.hhs.gov>

01/18/2011 06:41 AM

Dear Dr. Bray,

Thank you for your question regarding validation of different matrix types for your troponin assay. As indicated in the Points to Consider document from April 2010, we recommend that if you are pursuing more than a single matrix type claim for your device then you should collect and test specimens for each claimed sample matrix, such as whole blood and plasma, to obtain clearance for multiple matrices. If you decide not to include all claimed matrix types in your clinical performance evaluation, then you will need to demonstrate that there is little to no bias between sample types in a matrix comparison study using substantially narrow acceptance criteria. In addition, you will need to include an adequate number of samples around the assay cutoff. The results from your matrix comparison study will be evaluated during the review of your device premarket notification.

Do not hesitate to contact us if you have further questions.

Sincerely,

Ileana

Ileana Elder, Ph.D., RAC, CQA (ASQ)
FDA/CDRH/OIVD/DCTD
Phone: (301) 796-6143

As provided for in Dr. Elder's reply, we did not include all claimed matrix types in our clinical performance evaluation, but instead we demonstrated that there is little to no bias between serum and lithium heparin plasma used in the matrix comparison study. We tested matched serum and lithium heparin plasma specimens from 123 subjects whose TnI levels spanned the assay range.

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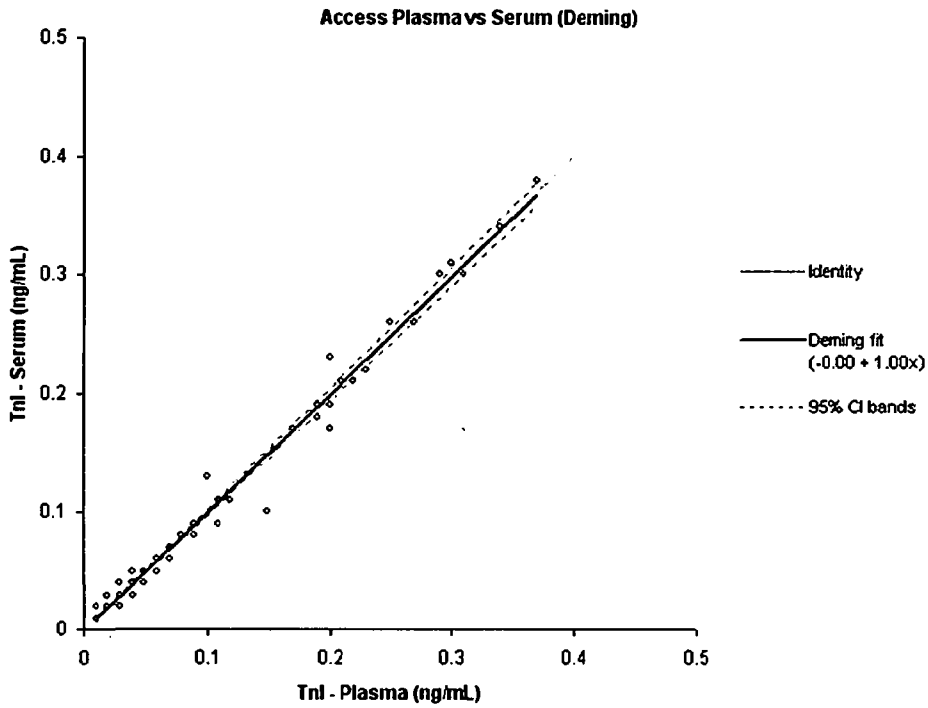
Analytical agreement between the two specimen types was originally tested by Passing-Bablok regression analysis for the 107 subjects whose TnI levels were above 0.01 ng/ml. The excellent agreement shown between the matrices for specimens from the pivotal study as documented in the 510(k) submission (n= 107, slope= 1.00, 95% CI= 0.98 – 1.00, Y intercept= 0.00, r= 1.00) demonstrated the equivalence of serum to plasma as sample matrices for the AccuTnI assay.

To address Dr. Elder's instruction that we focus on patients near the clinical cut off, we have performed a Deming regression analysis on those paired serum and plasma samples within the pivotal clinical trial with troponin levels from 0.01 to 0.4 ng/ml. Similar to what was observed in the wider range analysis, excellent agreement between the two matrices was observed. n= 86, slope= 1.00, Y intercept= 0.00, r= 0.99. See figure below:



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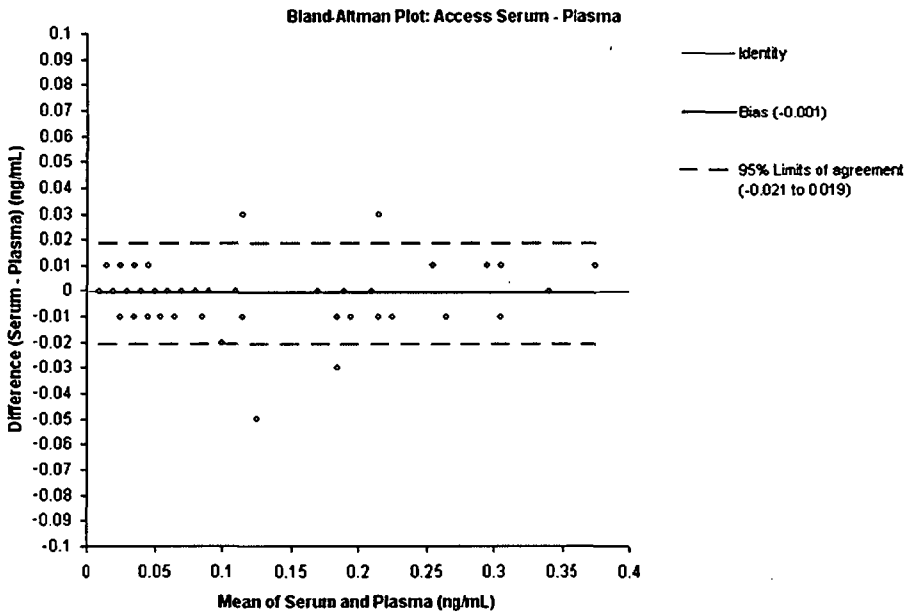
To further assess the agreement between the two matrix types, we also performed a Bland-Altman analysis of bias for the same specimens with values in the clinically-relevant range between 0.01 and 0.40 ng/ml. As the Bland-Altman plot below shows, there was only a small degree of random distribution around a near-zero bias (-0.001), indicating no systemic bias between the two sample matrix types.



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Next, to investigate the clinical concordance between the two sample types around the 0.03 ng/ml recommended clinical cut-off, we performed McNemar's test on the serum and plasma data from all 123 subjects for which both specimen types had been tested. The table below shows excellent concordance with no significant differences (p=0.65) between serum and lithium heparin plasma.

Access AccuTnI: Plasma vs Serum Concordance Analysis
McNemar's Test: p=0.65
96% agreement between plasma and serum (118/123)

	Serum <0.03	Serum ≥0.03	Total
Plasma <0.03	38 (30.9%)	3 (2.4%)	41 (33.3%)
Plasma ≥0.03	2 (1.6%)	80 (65.0%)	82 (66.7%)
Total	40 (32.5%)	83 (67.5%)	123 (100%)

Finally, to further examine the clinical utility of the matched serum and plasma specimens from the pivotal trial, we constructed Receiver Operating Characteristic curves (ROC) for each matrix using all subjects with both serum and plasma test results. As shown in the figure on the next page, the two specimen types showed equivalent diagnostic efficacy. The areas under the ROC curve (AUC) are **0.845** and **0.847** for plasma and serum, respectively.

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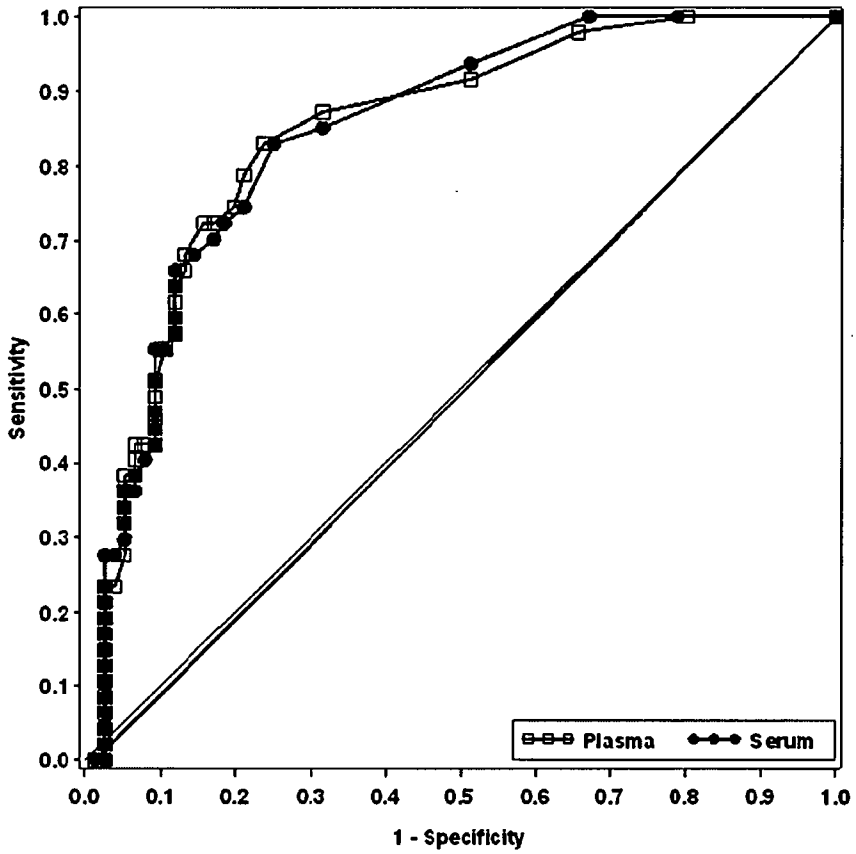
ROC Curves, Plasma vs. Serum
Study TnI - Access
Adjudicator Diagnosis



N_{MI}	$N_{Non\text{-}MI}$	Matrix	AUC	95% Confidence Interval	p-value
47	76	Plasma	0.845	0.775 - 0.916	0.876
.	.	Serum	0.847	0.778 - 0.915	
p-value for comparison of AUCs between serum vs. plasma samples					

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Following the direction from FDA, BEC has demonstrated a high degree of agreement in correlation, concordance, lack of bias, and equivalent diagnostic efficacy between serum and lithium heparin plasma for specimens both near the clinical cut-off and at higher levels. This high degree of agreement is confirmed by the results of the independent, internal analytical matrix comparison studies described in the 510(k) submission.

Therefore, we maintain that the data clearly justify the use of serum, and that the claim for both sample matrices be retained in our statement of Intended Use.

Natural, Unmodified Patient Sample Rationales

FDA Response: *We still recommend that you provide data for all requested studies using natural patient samples (i.e. not spiked with exogenous cTnI analyte). However, we agree that the use of pooled patient samples with relevant cTnI concentrations (that are not spiked with exogenous cTnI analyte) are acceptable for the requested studies (i.e., LoD, LoQ, field effectiveness studies and precision studies).*

BEC confirms that natural patient pools with relevant cTnI concentrations (i.e., not spiked with exogenous cTnI analyte) were used for LoD, LoQ, and precision studies.

Please review the Field Effectiveness study information provided below. BEC believes that the use of commercial quality control materials in these studies is appropriate, and that the results demonstrate the effectiveness of the thermal algorithm under a variety of system and field conditions. We will be prepared to discuss any additional questions you have regarding this topic.

The Field Effectiveness studies were requested by the Division, and were specifically designed to provide additional confidence that the final AccuTnI product in its entirety, including thermal algorithm, system software, assay protocol files, etc., performs properly on fielded instruments. The study design challenged the thermal algorithm under conditions of broader variability than is typically encountered in the clinical laboratory environment, including:

- Multiple instruments of varying vintage
- Multiple ambient temperatures, constant and dynamic
- Multiple reagent lots
- Multiple test request scenarios including STAT, panels, reflex, etc.
- Multiple test scenarios under random access conditions including other assays

Because of the large sample volumes needed for these studies, commercial quality control materials known to emulate natural patient sample thermal behavior were used for the Field Effectiveness studies at internal and external sites. We maintain that the use of natural patient samples in the field effectiveness studies is not necessary because accuracy, precision, and sensitivity of the assay were each verified using natural patient samples and/or pools in other studies conducted according to recognized guidelines. Therefore, the use of quality control

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materials known to emulate the patient samples in response to ambient temperature changes is entirely appropriate for this type of study.

We maintain that the Field Effectiveness studies, using commercial control materials and the wide range of variables included in the study design, provide objective evidence of the robustness of the assay and algorithm when used in a variety of system and field conditions.

Calibration Strategy

FDA response: *In addition to understanding "that even though the calibrator signals do not change with ambient temperature, the system can perform valid calibrations at the extremes of the temperature range with appropriate software algorithm adjustment of sample results", we need to understand the performance of the device as it is intended to be used. Regarding the limits of detection studies (i.e., LoB, LoD and LoQ) while we encourage different sources of variables in your studies, these should be within the context of the expected variability that the end user would experience. As such, it seems that calibrating at every temperature is not as this device is to be used. Therefore, in your response, please provide data for the requested studies demonstrating the performance of this device as intended for use. As discussed above in item 2, in your response, you need to demonstrate that the performance of your device is equivalent irrespective of ambient temperature and that your device is safe for patient use. Furthermore, where there are differences in the performance with calibration at each temperature compared to calibration at a single temperature, you should investigate the reason for the difference in the performance and provide your findings for FDA review.*

Please review the calibration information provided below. BEC believes that the calibration strategy used in these studies is appropriate, and the results demonstrate the effectiveness of the thermal algorithm. We will be prepared to discuss any additional questions you have regarding this topic.

As previously described, the thermal profile of calibrator material is distinct from patient samples and controls. Since the algorithm already accounts for the difference in thermal sensitivity between calibrators and samples, it is immaterial whether a sample is run at the same or different temperature from which the device was calibrated. Therefore, the device performance is not misrepresented in situations where the sample measurements are taken at the same temperature as calibration.

The effectiveness of the algorithm at different calibration temperatures is demonstrated by two independent studies, which allow data reduction from calibration curves generated at multiple, discrete temperatures. The complete datasets including reduction of data from multiple calibration temperature scenarios from "Thermal Sensitivity – Robustness" and "Thermal Sensitivity – Impact on Cross-Temperature Method Comparison," will be provided to the Division as part of our final 510(k) submission response.

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Analytical testing to establish assay detection capability (i.e., LoB, LoD) is fundamentally different from routine testing in the clinical laboratory. BEC's detection capability studies were conducted in conformance with the recognized CLSI guideline EP17-A2, "Detection Capability for Clinical Laboratory Measurement Procedures," and are specifically designed to establish these parameters, and *not* to duplicate end-user testing conditions.

EP17-A2 recommends that manufacturers include multiple reagent lots, multiple calibration cycles, and other variables to establish estimates of LoB, LoD or LoQ to "increase the rigor of the resulting detection capability estimates." If we were to run the study "as it is intended to be used" by the clinical laboratory, then we would sacrifice the rigor of the assay's performance estimates.

Nevertheless, Beckman will provide data and results from LoB, LoD, and LoQ studies where the calibration was performed at multiple temperatures, different from those at which measurements were taken, as part of our 510(k) submission response.

Therefore, we maintain that BEC's detection capability studies, with the added data analysis of multi-temperature calibrations, provide objective evidence for the detection performance claims included in the AccuTnI Instructions for Use.

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Appendix 5: Emails referred to in the Response to Question 4, Clinical matrix comparison study

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In correspondence with FDA, Beckman asked for specific clarification about requirements for validation of additional matrix types. In an e-mail to lead reviewer, Ileana Elder, dated January 13, 2011 we asked:

From: krbray@beckman.com [mailto:krbray@beckman.com]
Sent: Thursday, January 13, 2011 10:28 AM
To: Elder, Ileana
Subject: I100255

Dear Dr. Elder,

I am writing with a brief question concerning one point of our specimen testing plans for our ongoing prospective AccuTnI clinical trial for the Access and DxI assay systems.

Our current primary specimen type for TnI measurement is lithium heparin, but we also wish to validate the use of serum and include that in our labeling as well. Thus, consistent with the direction provided in FDA's "Points to Consider" document, and using CLSI guidance EP 09 as a guide, our plan is to test the lithium heparin specimens from entire clinical cohort. The use of serum will at the same time be validated per EP 09 by testing and comparing a sufficient subset of serum specimens from the relevant target clinical population enrolled in our clinical trial.

Please confirm that this approach is aligned with FDA's expectations for validation of multiple specimen types. Thank you.

Kurt Bray

Kurtis R. Bray, Ph.D.
Director of Clinical Research
Beckman Coulter, Inc.
2470 Faraday Avenue
Carlsbad, CA 92010

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Dr. Elder replied via e-mail on January 18, 2011:

"Elder, Ileana" <Ileana.Elder@fda.hhs.gov>
01/18/2011 06:41 AM

Dear Dr. Bray,
Thank you for your question regarding validation of different matrix types for your troponin assay. As indicated in the Points to Consider document from April 2010, we recommend that if you are pursuing more than a single matrix type claim for your device then you should collect and test specimens for each claimed sample matrix, such as whole blood and plasma, to obtain clearance for multiple matrices. If you decide not to include all claimed matrix types in your clinical performance evaluation, then you will need to demonstrate that there is little to no bias between sample types in a matrix comparison study using substantially narrow acceptance criteria. In addition, you will need to include an adequate number of samples around the assay cutoff. The results from your matrix comparison study will be evaluated during the review of your device premarket notification.
Do not hesitate to contact us if you have further questions.
Sincerely,
Ileana
Ileana Elder, Ph.D., RAC, CQA (ASQ)
FDA/CDRH/OIVD/DCTD
Phone: (301) 796-6143

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 6: Linearity results, including higher order fitted estimates, linearity plots, and difference tables referenced in the response to Question 6.c.

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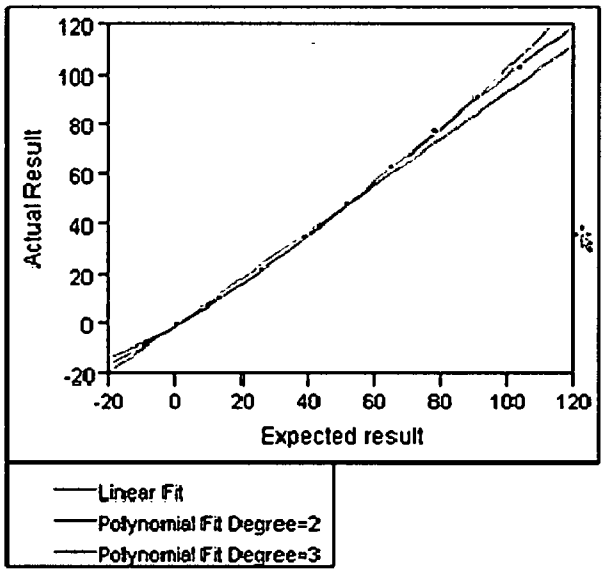
Table 1. Reagent Pack 225961, Instrument 500006, 18°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0006	0.4801
	X	0.9413	0.0000
2nd	Intercept	0.0020	0.0017
	X	0.8135	0.0000
	X^2	0.0022	0.0005
3rd	Intercept	0.0027	0.0003
	X	0.7495	0.0000
	X^2	0.0052	0.0025
	X^3	0.0000	0.0218



Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.011	0.011	0.011	0.0000	[redacted]
Sample 2	13.027	12.264	10.590	[redacted]	-14%
Sample 3	26.044	24.517	22.587	[redacted]	-8%
Sample 4	39.061	36.770	35.662	[redacted]	-3%
Sample 5	52.077	49.023	49.474	[redacted]	1%
Sample 6	65.094	61.276	63.680	[redacted]	4%
Sample 7	78.110	73.529	77.942	[redacted]	6%
Sample 8	91.127	85.782	91.917	[redacted]	7%
Sample 9 High	104.144	98.035	105.264	[redacted]	7%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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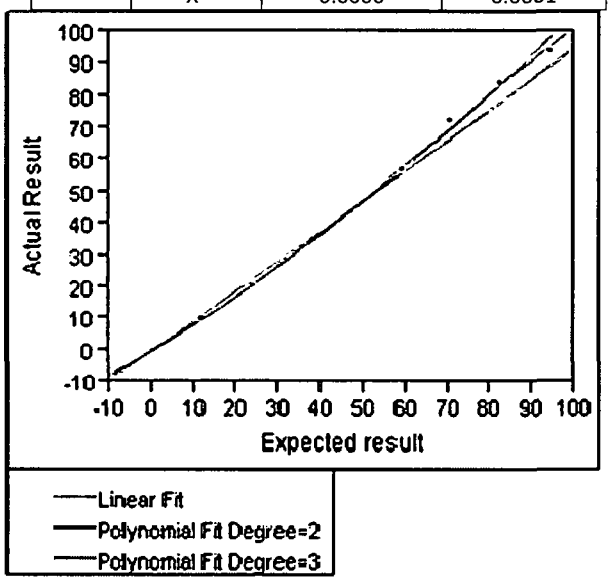
Table 2. Reagent Pack 225961, Instrument 504050, 18°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0003	0.5174
	X	0.9504	0.0000
2nd	Intercept	0.0012	0.0022
	X	0.8325	0.0000
	X^2	0.0022	0.0006
3rd	Intercept	0.0015	0.0012
	X	0.7796	0.0000
	X^2	0.0049	0.0087
	X^3	0.0000	0.0661



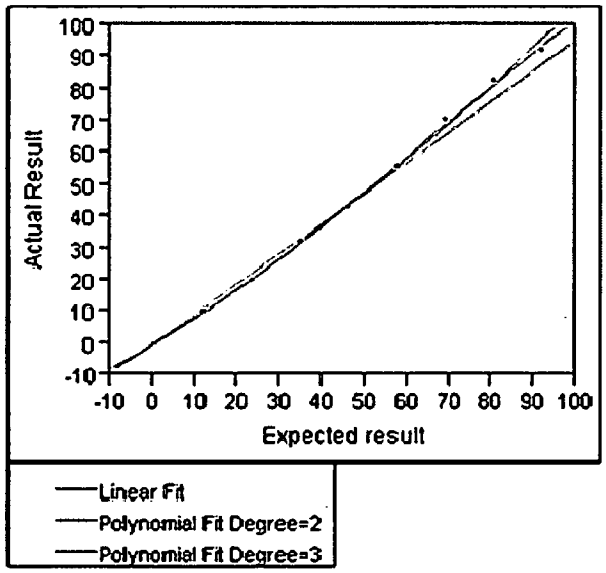
Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.007	0.007	0.007	0.0000	[redacted]
Sample 2	12.053	11.456	10.070	[redacted]	-12%
Sample 3	24.100	22.905	21.298	[redacted]	-7%
Sample 4	36.146	34.354	33.421	[redacted]	-3%
Sample 5	48.193	45.804	46.173	[redacted]	1%
Sample 6	60.239	57.253	59.283	[redacted]	4%
Sample 7	72.286	68.702	72.482	[redacted]	6%
Sample 8	84.332	80.151	85.503	[redacted]	7%
Sample 9 High	96.379	91.600	98.076	[redacted]	7%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 3. Reagent Pack 225962, Instrument 500006, 18°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0004	0.5410
	X	0.9554	0.0000
2nd	Intercept	0.0014	0.0031
	X	0.8435	0.0000
	X^2	0.0022	0.0008
3rd	Intercept	0.0019	0.0023
	X	0.7943	0.0000
	X^2	0.0047	0.0146
	X^3	0.0000	0.0975



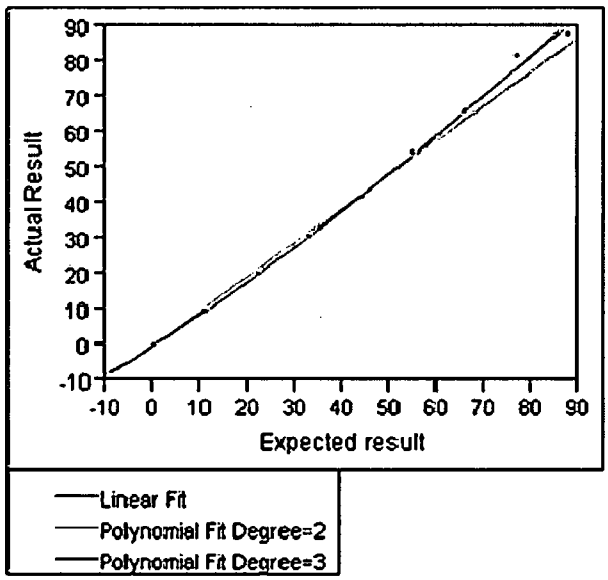
Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.009	0.009	0.009	0.0000	[redacted]
Sample 2	11.807	11.280	9.999	[redacted]	-11%
Sample 3	23.605	22.552	21.062	[redacted]	-7%
Sample 4	35.403	33.823	32.954	[redacted]	-3%
Sample 5	47.202	45.095	45.428	[redacted]	1%
Sample 6	59.000	56.366	58.241	[redacted]	3%
Sample 7	70.798	67.637	71.145	[redacted]	5%
Sample 8	82.596	78.909	83.897	[redacted]	6%
Sample 9 High	94.394	90.180	96.250	[redacted]	7%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 4. Reagent Pack 225962, Instrument 504050, 18°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0003	0.6267
	X	0.9676	0.0000
2nd	Intercept	0.0014	0.0090
	X	0.8678	0.0000
	X^2	0.0020	0.0019
3rd	Intercept	0.0018	0.0144
	X	0.8319	0.0000
	X^2	0.0040	0.0695
	X^3	0.0000	0.2976



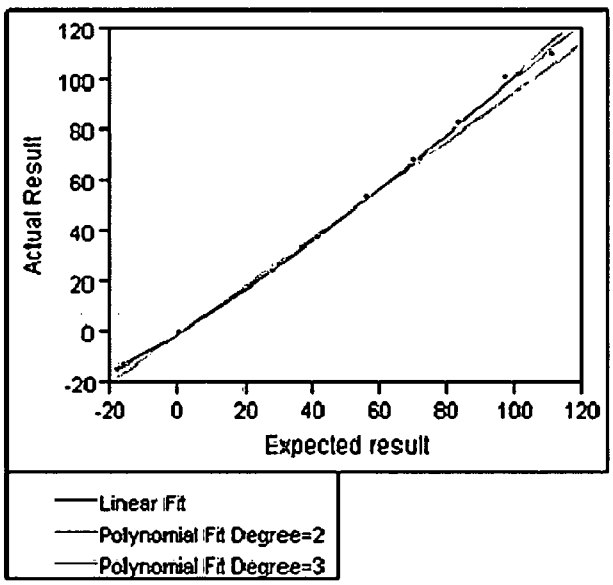
Sample	Expected (ng/mL)	Linear	Quadratic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.011	0.011	0.011	0.0000	[redacted]
Sample 2	11.345	10.977	10.106	[redacted]	-8%
Sample 3	22.679	21.944	20.721	[redacted]	-6%
Sample 4	34.013	32.910	31.857	[redacted]	-3%
Sample 5	45.347	43.877	43.512	[redacted]	-1%
Sample 6	56.682	54.843	55.688	[redacted]	2%
Sample 7	68.016	65.810	68.383	[redacted]	4%
Sample 8	79.350	76.776	81.599	[redacted]	6%
Sample 9 High	90.684	87.743	95.335	[redacted]	9%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 5. Reagent Pack 225961, Instrument 500006, NLC

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0002	0.5825
	X	0.9610	0.0000
2nd	Intercept	0.0007	0.0057
	X	0.8537	0.0000
	X^2	0.0017	0.0014
3rd	Intercept	0.0009	0.0070
	X	0.8106	0.0000
	X^2	0.0036	0.0387
	X^3	0.0000	0.1981



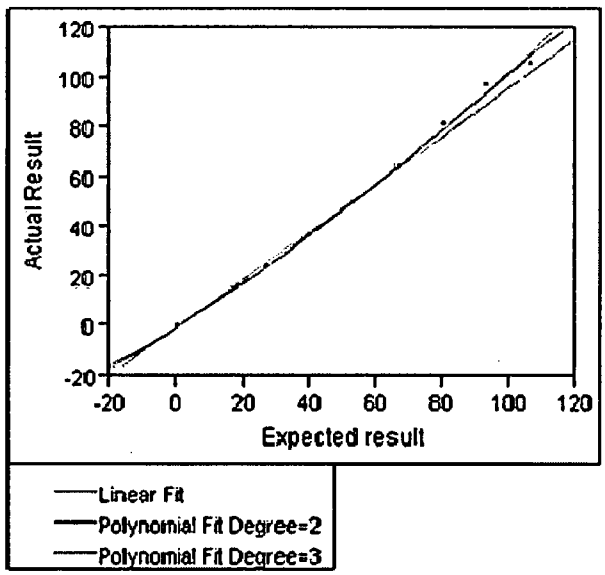
Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.005	0.005	0.005	0.0000	[redacted]
Sample 2	14.215	13.661	12.207	[redacted]	-11%
Sample 3	28.426	27.318	25.603	[redacted]	-6%
Sample 4	42.637	40.975	39.934	[redacted]	-3%
Sample 5	56.848	54.631	54.940	[redacted]	1%
Sample 6	71.058	68.288	70.364	[redacted]	3%
Sample 7	85.269	81.945	85.944	[redacted]	5%
Sample 8	99.480	95.601	101.424	[redacted]	6%
Sample 9 High	113.691	109.258	116.543	[redacted]	7%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 6. Reagent Pack 225961, Instrument 504050, NLC

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0001	0.5850
	X	0.9644	0.0000
2nd	Intercept	0.0003	0.0053
	X	0.8652	0.0000
	X^2	0.0017	0.0012
3rd	Intercept	0.0004	0.0105
	X	0.8334	0.0000
	X^2	0.0031	0.0636
	X^3	0.0000	0.3100



Sample	Expected (ng/mL)	Linear	Quadratic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.003	0.003	0.003	0.0000	[redacted]
Sample 2	13.746	13.257	12.208	[redacted]	-8%
Sample 3	27.490	26.511	25.042	[redacted]	-6%
Sample 4	41.234	39.765	38.505	[redacted]	-3%
Sample 5	54.978	53.019	52.595	[redacted]	-1%
Sample 6	68.721	66.273	67.314	[redacted]	2%
Sample 7	82.465	79.527	82.662	[redacted]	4%
Sample 8	96.209	92.781	98.638	[redacted]	6%
Sample 9 High	109.953	106.035	115.242	[redacted]	9%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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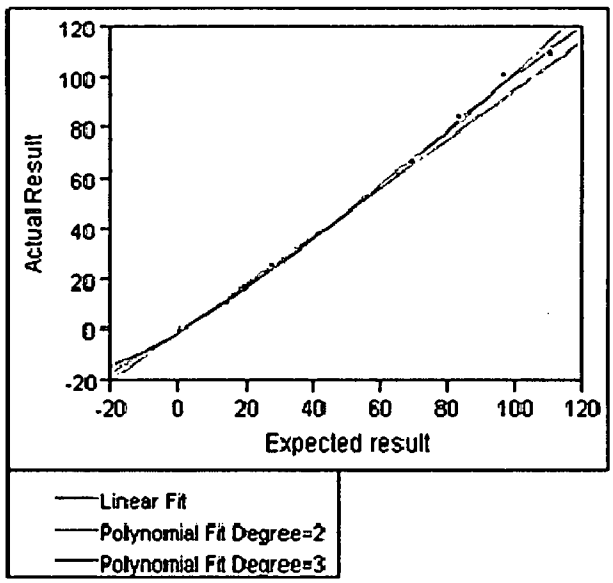
Table 7. Reagent Pack 225962, Instrument 500006, NLC

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0005	0.6272
	X	0.9628	0.0000
2nd	Intercept	0.0019	0.0158
	X	0.8513	0.0000
	X^2	0.0018	0.0038
3rd	Intercept	0.0028	0.0080
	X	0.7862	0.0000
	X^2	0.0046	0.0278
	X^3	0.0000	0.1123



Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.013	0.013	0.013	0.0000	[redacted]
Sample 2	14.303	13.771	12.127	[redacted]	-12%
Sample 3	28.592	27.528	25.735	[redacted]	-7%
Sample 4	42.882	41.286	40.434	[redacted]	-2%
Sample 5	57.171	55.044	55.824	[redacted]	1%
Sample 6	71.461	68.802	71.504	[redacted]	4%
Sample 7	85.750	82.560	87.073	[redacted]	5%
Sample 8	100.040	96.317	102.128	[redacted]	6%
Sample 9 High	114.329	110.075	116.270	[redacted]	6%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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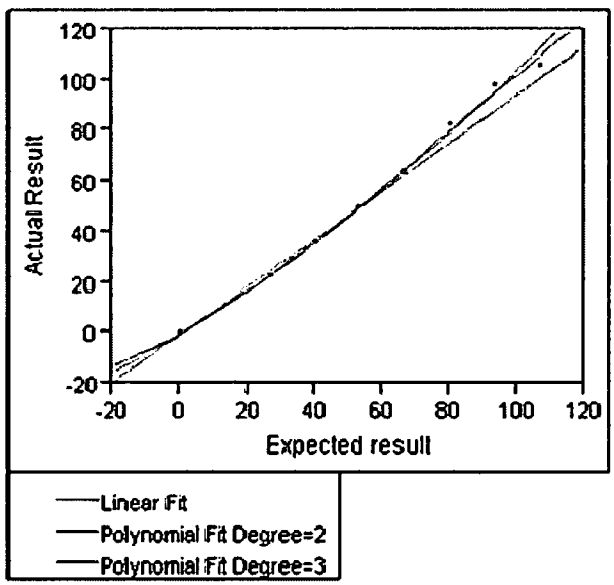
Table 8. Reagent Pack 225962, Instrument 504050, NLC

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0008	0.5742
	X	0.9479	0.0000
2nd	Intercept	0.0029	0.0035
	X	0.8059	0.0000
	X^2	0.0024	0.0008
3rd	Intercept	0.0038	0.0039
	X	0.7495	0.0000
	X^2	0.0049	0.0241
	X^3	0.0000	0.1514



Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.015	0.015	0.015	0.0000	[redacted]
Sample 2	13.942	13.216	11.350	[redacted]	-14%
Sample 3	27.868	26.418	24.248	[redacted]	-8%
Sample 4	41.795	39.619	38.364	[redacted]	-3%
Sample 5	55.722	52.820	53.354	[redacted]	1%
Sample 6	69.649	66.021	68.874	[redacted]	4%
Sample 7	83.575	79.223	84.579	[redacted]	7%
Sample 8	97.502	92.424	100.124	[redacted]	8%
Sample 9 High	111.429	105.625	115.165	[redacted]	9%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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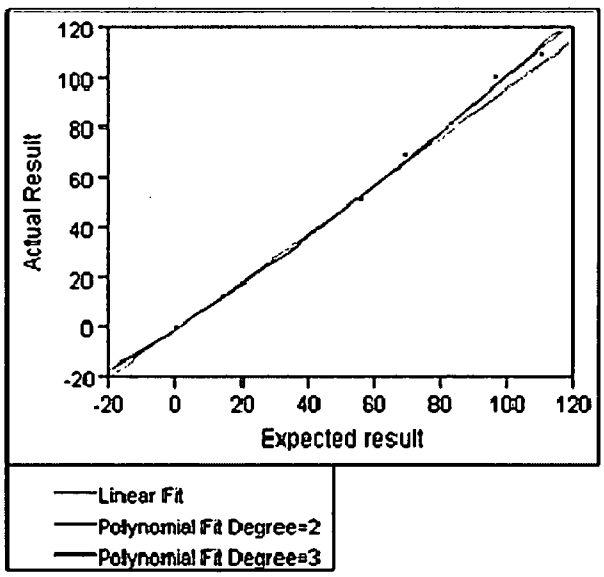
Table 9. Reagent Pack 225961, Instrument 500006, 28°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0010	0.5722
	X	0.9670	0.0000
2nd	Intercept	0.0035	0.0080
	X	0.8804	0.0000
	X^2	0.0014	0.0021
3rd	Intercept	0.0042	0.0212
	X	0.8578	0.0000
	X^2	0.0024	0.1245
	X^3	0.0000	0.4701



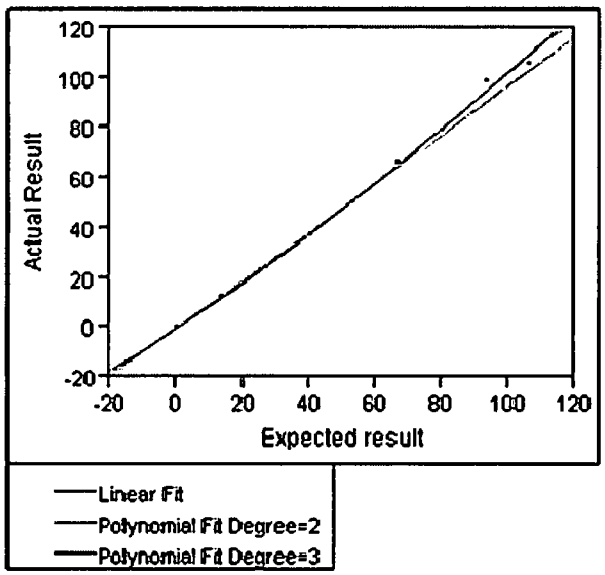
Sample	Expected (ng/mL)	Linear	Quadratic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.030	0.030	0.030	0.0000	[redacted]
Sample 2	14.054	13.592	12.652	[redacted]	-7%
Sample 3	28.079	27.154	25.826	[redacted]	-5%
Sample 4	42.103	40.717	39.550	[redacted]	-3%
Sample 5	56.128	54.279	53.825	[redacted]	-1%
Sample 6	70.152	67.841	68.651	[redacted]	1%
Sample 7	84.177	81.403	84.027	[redacted]	3%
Sample 8	98.201	94.966	99.954	[redacted]	5%
Sample 9 High	112.226	108.528	116.432	[redacted]	7%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 10. Reagent Pack 225961, Instrument 504050, 28°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0007	0.6683
	X	0.9754	0.0000
2nd	Intercept	0.0032	0.0214
	X	0.8928	0.0000
	X^2	0.0014	0.0048
3rd	Intercept	0.0037	0.0531
	X	0.8741	0.0000
	X^2	0.0022	0.2123
	X^3	0.0000	0.6024



Sample	Expected (ng/mL)	Linear	Quadratic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.030	0.030	0.030	0.0000	[redacted]
Sample 2	13.757	13.419	12.546	[redacted]	-7%
Sample 3	27.485	26.809	25.583	[redacted]	-5%
Sample 4	41.212	40.199	39.140	[redacted]	-3%
Sample 5	54.940	53.588	53.218	[redacted]	-1%
Sample 6	68.667	66.978	67.815	[redacted]	1%
Sample 7	82.395	80.368	82.933	[redacted]	3%
Sample 8	96.123	93.758	98.572	[redacted]	5%
Sample 9 High	109.850	107.147	114.731	[redacted]	7%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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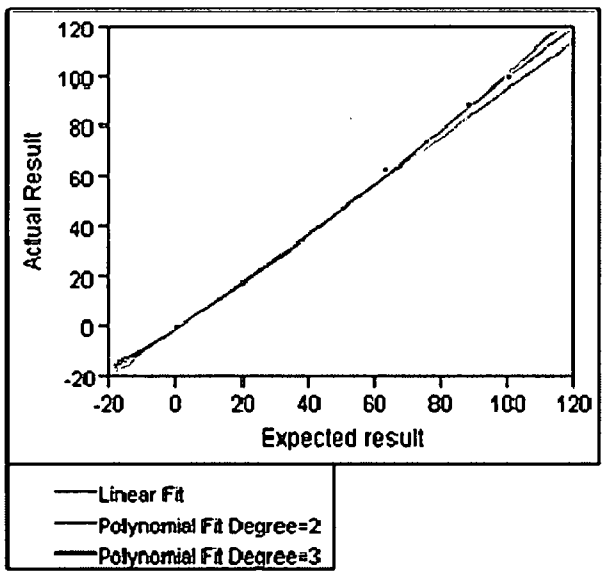
Table 11. Reagent Pack 225962, Instrument 500006, 28°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0002	0.4676
	X	0.9596	0.0000
2nd	Intercept	0.0007	0.0033
	X	0.8759	0.0000
	X^2	0.0015	0.0011
3rd	Intercept	0.0009	0.0047
	X	0.8431	0.0000
	X^2	0.0031	0.0359
	X^3	0.0000	0.1938



Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.006	0.006	0.006	0.0000	[redacted]
Sample 2	12.534	12.029	11.021	[redacted]	-8%
Sample 3	25.062	24.051	22.832	[redacted]	-5%
Sample 4	37.591	36.074	35.274	[redacted]	-2%
Sample 5	50.119	48.097	48.182	[redacted]	0%
Sample 6	62.647	60.120	61.392	[redacted]	2%
Sample 7	75.176	72.143	74.739	[redacted]	4%
Sample 8	87.704	84.165	88.058	[redacted]	5%
Sample 9 High	100.233	96.188	101.184	[redacted]	5%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 9: Instructions for Use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG;

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- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination.

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Store and dispose of these materials and their containers in accordance with local regulations and guidelines.

- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
107	0.01–20	0.00 (0.00–0.00)	1.00 (0.98–1.00)	1.00
104	0.01–5	0.00 (0.00–0.00)	1.00 (1.00–1.00)	1.00

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

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Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

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Limitations of the Procedure

1. This product is for use on Access 2 systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing.
3. Samples can be accurately measured within the analytical range of the assay (approximately 0.01–100 ng/mL [µg/L]).
   - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value (i.e., < 0.01 ng/mL [µg/L]).
   - If a sample contains more than the stated value of the highest Access AccuTnI+3 Calibrator (S5), report the result as greater than that value (i.e., > 100 ng/mL [µg/L]).
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[21,22] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[23,24] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[25] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
7. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
8. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Each laboratory should establish its own reference ranges to assure proper representation of specific populations and sample types, and to reflect current practice at their institutions.

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.

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- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[26] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, and ≥ 3 – 6 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed

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the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94 – 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility. Each facility should evaluate prevalence at their institution and adjust PPV and NPV accordingly.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility. Each facility should determine prevalence at their institution and adjust PPV and NPV accordingly.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 system. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of < 16% for samples > 0.105 ng/mL (μg/L), and < 0.0168 ng/mL (μg/L) for samples ≤ 0.105 ng/mL (μg/L).

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Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations greater than 0.105 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.0084 ng/mL (µg/L) at concentrations ≤ 0.105 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used two patient pools and three commercial controls, tested in duplicate in two runs per shift, two shifts per day, over a minimum of 10 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Patient Pool	0.07	5.0	5.0	7.1
Commercial Control 1	0.91	2.0	5.0	5.4
Commercial Control 2	1.96	2.2	4.9	5.3
Commercial Control 3	13.97	2.3	4.7	5.2
High Patient Pool	56.36	5.1	3.9	6.4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added	Substance	Highest Concentration Added
Acetaminophen	20 mg/dL	**Furosemide**	40 mg/dL
Acetylsalicylic Acid	65 mg/dL	**Hemoglobin**	5 mg/mL
Allopurinol	40 mg/dL	**Human Serum Albumin**	6000 mg/dL
Ambroxol	40 mg/dL	**Ibuprofen**	50 mg/dL
Ampicillin	5 mg/dL	**Low MW Heparin**	71 µg/mL
Ascorbic Acid	6 mg/dL	**Methyldopa**	2.5 mg/dL
Atenolol	1 mg/dL	**Nifedipine**	6 µg/dL
Bilirubin (conjugated)	40 mg/dL	**Nitrofurantoin**	6.4 mg/dL
Bilirubin (unconjugated)	40 mg/dL	**Nystatin**	2.15 mg/dL
Biotin	290 ng/mL	**Oxytetracycline**	24 mg/dL
Caffeine	10 mg/dL	**Phenytoin**	10 mg/dL
Captopril	5 mg/dL	**Propranolol**	500 µg/mL
Cinnarizine	40 mg/dL	**Quinidine**	2 mg/dL
Cocaine	2 mg/dL	**Simvastatin**	200 µg/mL
Diclofenac	5 mg/dL	**Theophylline**	25 mg/dL
Digoxin	200 ng/mL	**Triglycerides**	3000 mg/dL
Dopamine	48.75 mg/dL	**Trimethoprim**	7.5 mg/dL
Erythromycin	20 mg/dL	**Verapamil**	16 mg/dL
Fibrinogen	1000 mg/dL	**Warfarin**	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.

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Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A.[35] A total number of 156 replicates of a zero analyte sample (S0 calibrator) were measured in 12 runs using multiple reagent and calibrator lots on three Access 2 systems.

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.005 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A.[35] Three replicates from five low-level heparin plasma samples were measured using multiple reagent and calibrator lots in 12 runs on three Access 2 systems.

Limit of Quantitation

Nine experiments containing seven samples for a total of sixty-three imprecision estimates, based on CLSI EP17-A,[35] were performed to determine the Limit of Quantitation (LoQ) of the Access AccuTnI+3 assay. Each study tested a sample in triplicate, in two runs per shift, two shifts per day, over a minimum of 10 days using one Access 2 system and one reagent lot. In the nine experiments a total of six Access 2 systems, three lots of reagents, and two calibrator lots were used.

To estimate the expected imprecision in the clinically relevant concentration range, study results were sorted by concentration. The lowest concentration sample with </= the expected imprecision (10% or 20%) determined the LoQ. The Access AccuTnI+3 LoQ was 0.03 ng/mL (µg/L) at 10% CV and 0.02 ng/mL (µg/L) at 20% CV.

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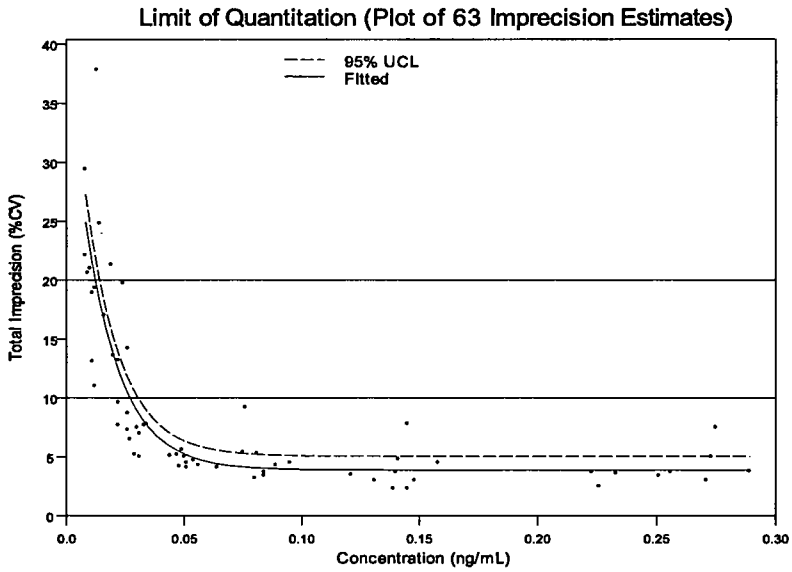

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Beckman Coulter, Inc.
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Brea, CA 92821 U.S.A.

Printed in U.S.A.
Made in U.S.A.
Issued December 2012

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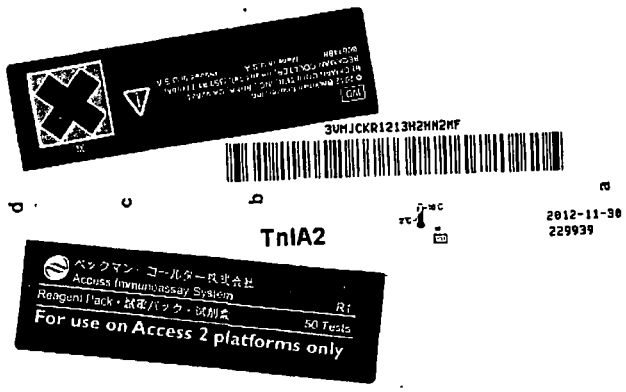
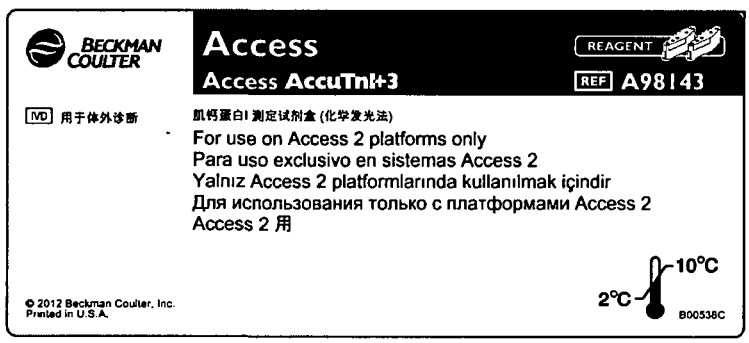
Appendix 10: Device Labeling

Access AccuTnI+3 Reagent Pack Top Label:



Access AccuTnI+3 Reagent Pack Package Labels:



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

Access ベックマン・コールター株式会社 REAGENT

Access AccuTnI+3 REF A98143

Access REAGENT II

Access AccuTnI+3

2 x 50 Tests/回用

R1a: 3.25 mL	Paramagnetic particles coated with mouse monoclonal anti-human cTnI, TRIS, surfactant, BSA.	固相試薬：磁性粒子結合抗ヒトトロポニンＩマウスモノクローナル抗体
R1b 9.95 mL	0.1 N NaOH	プローブ洗浄液：水酸化ナトリウム
R1c: 3.10 mL	TRIS buffered saline with surfactant.	緩衝液：トリス緩衝液
R1d: 3.10 mL	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, ACES, surfactant, protein (bovine, goat, mouse).	コンジュゲート試薬：アルカリホスファターゼ結合抗ヒトトロポニンＩマウスモノクローナル抗体

LOT

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体外診断用医薬品

B00539B

CE

Access

Access AccuTnI+3

REAGENT

REF A98143

2 reagent packs R1, for the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.

2 envases de reactivos R1, para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.

Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini niceliksel olarak tespit etmek için 2 reaktif paketi R1.

2 комплекта реагентов R1 для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.

クラスIII生化学・免疫・内分泌検査用シリーズ　トロポニンキット　/　アクセス AccuTnI 試薬パック

Xi, ≥ 0.0375 – < 1.5% ProClin* 300
R 43, S 28-37

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Access AccuTnI+3 Calibrator Package Labels:

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Access

CALIBRATORS S0 S1 S2 S3 S4 S5

Access AccuTnI+3 CALIBRATORS REF A98144

IVD 用于体外诊断

肌钙蛋白I校准品

For use on Access 2 platforms only
Para uso exclusivo en sistemas Access 2
Yalnız Access 2 platformlarında kullanılmak içindir
Для использования только с платформами Access 2
Access 2 用

-20°C

[1] 2–10°C after opening / après ouverture / después de abrir / dopo l'apertura / nach dem Öffnen / após a abertura / after öppning / after åbning / po otwarciu / Açıldıktan sonra / после вскрытия / Avaamisen jälkeen / 開封後は保存 / 开封后储存 / etter at den er åpnet / Съхранение на след отваряне

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B00535C

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Access

CALIBRATORS S0 S1 S2 S3 S4 S5

Access AccuTnI+3 CALIBRATORS REF A98144

Access CALIBRATORS II

Access AccuTnI+3 CALIBRATORS

LOT

1 x 1.5 mL	S0	BSA matrix, surfactant.	ウシ血清アルブミン
1 x 1.5 mL	S1	BSA matrix, surfactant, recombinant cTnI.	リコンビナント心筋由来トロポニン複合体，ウシ血清アルブミン
4 x 1.0 mL	S2–S5	BSA matrix, surfactant, recombinant cTnI.	リコンビナント心筋由来トロポニン複合体，ウシ血清アルブミン

1 Calibration Card/Carte d'étalonnage/Tarjeta de calibración/Scheda di taratura/Kalibratorkarte/Cartão de calibração/Kalibreringskort/Kercle kalibracji/Kalibrasyon kartı/Калибровочная карта/Kalibravimo korteleje/キャリブレーションカード / 定标卡。/Калибрационна карта

S0: 0 ng/mL 0 µg/L	S1: ~0.3 ng/mL ~0.3 µg/L	S2: ~1.2 ng/mL ~1.2 µg/L	S3: ~5.0 ng/mL ~5.0 µg/L	S4: ~25 ng/mL ~25 µg/L	S5: ~100 ng/mL ~100 µg/L

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B00536C

CE

Access

CALIBRATORS S0 S1 S2 S3 S4 S5

Access AccuTnI+3 CALIBRATORS REF A98144

CALIBRATORS	For the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.
CALIBRADORES	Para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.
KALİBRATÖRLER	Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini niceliksel olarak tespit etmek için.
КАЛИБРАТОРЫ	Для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.
キャリブレータ	トロポニンキット用 / アクセス AccuTnI キャリブレータ

Xi, ≥ 0.0375 – < 1.5% ProClin* 300
R 43, S 28-37

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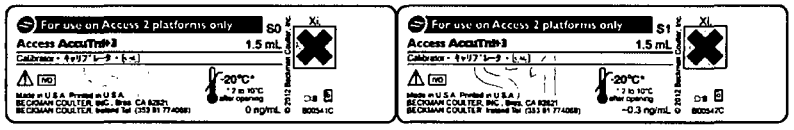
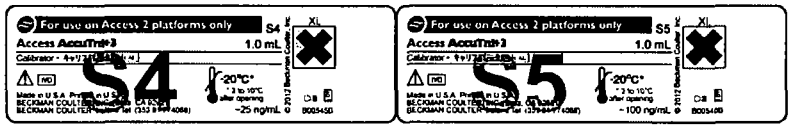
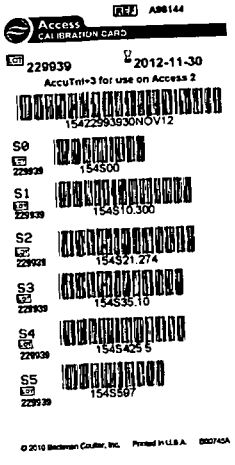
Access AccuTnI+3 Calibrator Vial Labels:





Access AccuTnI+3 Calibration Card:



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 11: Abbreviated 510(k) for AccuTnI+3 Calibrators

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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AccuTnI+3 Calibrator

Abbreviated Calibrator 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Required Elements Checklist

Section 510(k) element	Section
Proprietary and Established name	I
Intended Use	II
Summary and explanation	II
Test Principle	II
Matrix base	II
Constituents	II
Appropriate standardization/traceability	IV d
Warning and precautions	III
Appropriate testing of human source material	III
"For In Vitro Diagnostic Use" statement	III
Assigned values and value assignment process	IV b
Storage instructions / stability	III
Directions for Use	III
Limitations	III
Bibliography / references	III
Name and place of manufacturer	III
Date of Labeling	III

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GENERAL INFORMATION

Contact Information

Applicant's Name and Address	Beckman Coulter, Inc. 1000 Lake Hazeltine Dr. Chaska, MN 55318
Contact	Valynda Machen, Group Manager, Regulatory Affairs Ph: (952) 368-1383 Fax: (952) 368-7610 E-mail: vmachen@beckman.com
Establishment Registration Number	2122870

Device Information

Purpose for Submission

The Access AccuTnI+3 Calibrators will be used with the new AccuTnI+3 assay on the Access 2 Immunoassay Systems.

I. Device Description

Proprietary Name	AccuTnI+3 Calibrators on the Access 2 Immunoassay Systems
Common Name	Calibrator
Classification Number and Name	21 CFR §862.1150, Calibrator
Panel and Product Code	JIT
Device Classification	Class II
Measurand	Manufacturer's working Calibrators
Type of Test	Quantitative; enzyme immunoassay (EIA)
Predicate	ADVIA Centaur® TnI-Ultra™ (K053020)

The Access AccuTnI+3 Calibrators are a six-level calibrator set intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems. The calibrator set provides calibrators at six levels – zero and approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve). The calibrators contain a recombinant troponin complex in buffered BSA (bovine serum albumin).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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- Level S0; buffered bovine serum albumin matrix with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.
- Levels S1 – S5; recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL in buffered BSA matrix with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

The calibrators are contained in 6 mL vials, for S0 – S1the fill level is 1.5 mL and for S2 – S5 the fill level is 1.0 mL. The calibrator vials are intended for storage at -20°C or colder.

Calibration cards are provided with each calibrator kit. Calibration cards contain bar codes that are encrypted with the individual calibrator concentrations for each calibrator level.

II. Indication for Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infraction.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

III. **Labeling**

Access AccuTnI+3 Calibrator Instructions for Use

Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 SYSTEMS WITH TEST NAME: TnIA2

Intended Use The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information **Access AccuTnI+3 Calibrators (for use on Access 2 systems)**
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[13]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access Calibrators:

Calibrator Package Labels

BECKMAN COULTER

Access

CALIBRATORS

Access AccuTnI+3 CALIBRATORS REF A98144

IVD 用于体外诊断

肌钙蛋白I校准品

For use on Access 2 platforms only
Para uso exclusivo en sistemas Access 2
Yalnız Access 2 platformlarında kullanılmak içindir
Для использования только с платформами Access 2
Access 2 用

* 2-10°C after opening / après ouverture / después de abrir / dopo l'apertura / nach dem Öffnen / após a abertura / efter öppning / efter åbning / po otwarciu / Açıldıktan sonra / после вскрытия / Avdarius takyti / 開封後は保存 / 开封后保存 / efter at den er åbnet / съхранение на след отваряне

-20°C

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B00535C

BECKMAN COULTER

Access

CALIBRATORS

Access AccuTnI+3 CALIBRATORS REF A98144

Access CALIBRATORS II

Access AccuTnI+3 CALIBRATORS

1 x 1.5 mL	S0	BSA matrix, surfactant.	ウシ血清アルブミン
1 x 1.5 mL	S1	BSA matrix, surfactant, recombinant cTnI.	リコンビナント心筋由来トロポニン複合体，ウシ血清アルブミン
4 x 1.0 mL	S2–S5	BSA matrix, surfactant, recombinant cTnI.	リコンビナント心筋由来トロポニン複合体，ウシ血清アルブミン

1 Calibration Card/Carte d'étalonnage/Tarjeta de calibración/Scheda di taratura/Kalibratorkarte/Cartão de calibração/Kalibreringskort/Karcie kalibracji/Kalibrasyon kartı/Калибровочная карта/Kalibravimo kortelė/キャリブレーションカード / 定标卡。/Калибрационна карта

S0: 0 ng/mL 0 µg/L | S1: ~0.3 ng/mL ~0.3 µg/L | S2: ~1.2 ng/mL ~1.2 µg/L | S3: ~5.0 ng/mL ~5.0 µg/L | S4: ~25 ng/mL ~25 µg/L | S5: ~100 ng/mL ~100 µg/L

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B00536C

CE

Access

CALIBRATORS

Access AccuTnI+3 CALIBRATORS REF A98144

CALIBRATORS	For the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.
CALIBRADORES	Para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.
KALİBRATÖRLER	Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini nicaliksel olarak tespit etmek için.
КАЛИБРАТОРЫ	Для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.
キャリブレータ	トロポニンキット用 / アクセス AccuTnI キャリブレータ

Xi, ≥ 0.0375 – < 1.5% ProClin* 300
R 43, S 28-37

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B00537B

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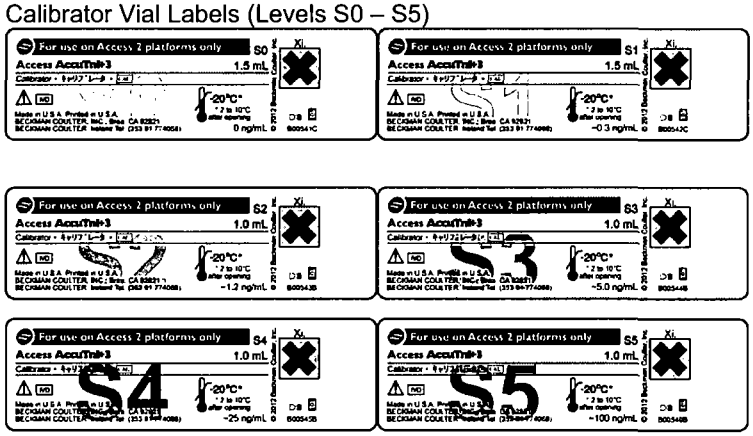
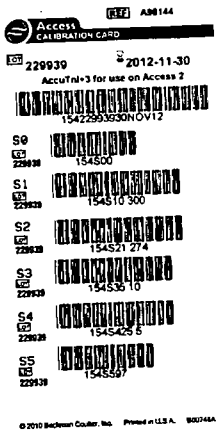
Calibrator Vial Labels (Levels S0 – S5)



Calibration Card



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Instructions for Use Reference Section

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Printed in U.S.A.
Made in U.S.A.
Issued November 2012

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IV. Summary Report

a. Description of Real Time and Accelerated Stability Studies is located in response Question 18.

b. Calibrator Preparation, value assignment and validation

Individual commercial calibrators are prepared using recombinant TnI-C and buffered BSA based matrix. The commercial calibrators are value assigned using the primary reference calibrators and the resulting calibrator values are provided to the customers on a calibrator card, which can be bar-code read directly into the Access immunoassay analyzers.

The manufacturing process requires the use of the primary reference calibrators, the newly manufactured commercial calibrators, commercial controls, and QC patient samples. Values for the newly manufactured commercial calibrators are determined from the primary reference curves. A nested design is utilized (alternating reference and test material) to generate values for the commercial calibrators using up to two reagent pack lots on one Access 2 instrument. Six replicates of S0 and 12 replicates of S1-S5 are averaged to generate the value assigned for each commercial calibrator level. Each lot's unique value assignment is verified on a single Access 2, running calibrator curves on reference and test material in a nested format. The resulting calibrator curves are used to generate dose values from a set of pre-specified RLUs (Relative Light Units). The test and reference curve doses are compared to a 95% confidence specification. Dose values for commercial calibrators must fall within quality control ranges. Control and QC patient samples are measured from the new assigned commercial calibrators and must meet QC specifications.

Calibration Results

During testing of the pilot lot of AccuTnI calibrators, the mean AccuTnI +3, the 95% confidence interval of the assay result was accurate within 0.0084SD of the primary calibrators for level S1 and 8% of the primary calibrators at levels S2-S5. See Table I for results.

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(b)(4) Testing

[redacted]

c. Specific number of instruments – see section IV b.

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d. Calibrator Traceability

The Access AccuTnI+3 Calibrators are not standardized to an international standard. The calibrators are standardized to an internal standard (Dade Stratus II TnI Assay) listed below.

There has been no changes implemented in the AccuTnI+3 Calibrator material as part of this submission; the antigen, the matrix and the concentration of the antigen at each level are identical to the previously cleared (k010429) Access AccuTnI Calibrators. A detailed description of the Calibrator Standardization is provided below:

The measurand (analyte) in the Access AccuTnI+3 Calibrators is recombinant single chain troponin IC complex (rscTnIC).

A rscTnIC standard stock was prepared at 500 ng/mL by dilution in AccuTnI Calibrator Matrix, based on the vendor's stated protein concentration (Bradford method).

The rscTnIC stock was assigned a value of 1300 ng/mL by harmonization to Dade Stratus II TnI Assay via value transference of patient sample results (from predicate) to rscTnIC standard stock dilutions in AccuTnI Calibrator Matrix. The adjustment factor applied to the vendor stated concentration of the rscTnIC antigen was determined to be 2.6.

For the harmonization activity, 140 lithium heparin samples were tested on the Dade Stratus II TnI assay.

136 dose results were readable in the range of the Dade Stratus II TnI assay and 88 of these samples had a duplicate measure from a 2nd Dade Stratus II TnI assay kit lot.

The 136 lithium heparin samples were run in replicates of 2 along with 9 dilutions of rscTnIC standard stock in AccuTnI Calibrator Matrix (and Calibrator matrix without antigen) in reps of 6 in one AccuTnI reagent lot.

After the rscTnIC antigen stock was reassigned, manufacturer's working calibrators were prepared to the following concentration levels 0, 0.3, 1.2, 5, 25 and 100 ng/mL.

e. Methodology for transferring performance of primary calibrators to the secondary calibrators is listed in section IV b.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 12: 510(k) Summary and Indications for Use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is k121214

Submitted By:

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1142
Fax: (952) 368-7610

Contact Person:

Valynda Machen
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1383
Fax: (952) 368-7610

Date Prepared:

December 12, 2012

Device Name:

Proprietary / Trade Name: Access AccuTnI+3 Reagent and Calibrator for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160

Predicate Devices:

The Access AccuTnI+3 assay and calibrators claim substantial equivalence to the TnI-Ultra™ Assay and Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Device Description:

The Access AccuTnI+3 reagents, AccuTnI+3 calibrators and the Access 2 Instrument compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI+3 reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

Intended Use:

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI+3 and the predicate device, ADVIA Centaur® TnI-Ultra™, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Similarities between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same

Differences between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized : high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 30 ng/mL	0.01 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.78 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.03 ng/mL	Total CV of ≤8% at concentrations >0.105 ng/mL. SD ≤0.0084 at concentrations ≤0.105 ng/mL
Indications for	The ADVIA Centaur® TnI-Ultra (TnI	The Access AccuTnI+3 assay is a

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3
Use Statement	Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Indication for Use	The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Calibrator for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

_____

Division Sign-Off

Office of In Vitro Diagnostic Device

Evaluation and Safety

510(k)_____

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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K121214 V.2

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

July 17, 2012

BECKMAN COULTER, INC.
1000 LAKE HAZELTINE DR.
CHASKA, MINNESOTA 55318-1084
ATTN: VALYNDA MACHEN

510k Number: K121214

Product: ACCESS ACCUTNL REAGENT AND CAL

Extended Until: 12/17/2012

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Director, 510(k) Program
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

July 13, 2012

FDA CDRH DMC
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U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
ATTN: Paula Velasco Caposino, Ph.D

SUBJECT: **K121214 Request for Extension**
Access AccuTnI on the Access 2 Immunoassay Systems

Dear Dr. Caposino,

Beckman Coulter, Inc. would like to request an extension for K121214 until December 17, 2012. This 180-day extension is needed to provide a comprehensive response to the FDA information request dated June 20, 2012.

If you have any questions regarding this request, please contact me by telephone at (952) 368-1383, by fax at (952) 368-7610, or by e-mail at vmachen@beckman.com.

Sincerely yours,

Valynda Machen, CQA, RAC
Group Manager Regulatory Affairs
Beckman Coulter, Inc.

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MEMORANDUM

To: File
From: Paula V. Caposino, Scientific Reviewer, DCTD/OIVD/CDRH/FDA
RE: k121214
Date: June 20, 2012

Based on discussion with Courtney Lias (Division Director, DCTD/OIVD), Jacqueline Wieneke (Medical Officer, OIVD/DCTD), Chava Zibman (Mathematical Statistician, OSB/DBS/DDB), Ruth Chesler (Associate Division Director, DCTD/OIVD), and my review of the submission, I recommend that we place k121214 on hold. The items listed below are needed to complete the review of the submission.

1. Thermal Sensitivity: You performed 3 studies to assess the effect of ambient temperature on the AccuTnI assay performance. We have the following concerns with your studies:
   a. Thermal Sensitivity-Impact on Low Dose Concordance/Agreement: Two hundred twenty lithium heparin plasma samples near the clinical cutoff were tested using 2 reagent lots on 2 instruments at 18, 20, 22, 24, 26 and 28°C ± 2°C. Each sample was divided into 3 aliquots and tested at either 18, 22 and 26°C or 20, 24 and 28°C. At each temperature, each sample was run in replicates of 2. A McNemar analysis was performed to determine whether the number of mismatched comparisons was due to random scatter or a systematic difference. In addition, bias between low and high temperature was computed using a log-log regression fit. Your acceptance criteria were that the McNemar p-value must be non-significant (≥0.05). If the p-value is significant, concordance must be ≥90%. Bias at the cutoffs must be ≤0.0084. Please address the following:
      i. You concluded that, in all comparisons of measurements taken on the same sample at different temperatures (averaging the duplicates taken for each measurement), there was agreement in 91% of the cases in terms of whether the values fell >0.03 or ≤0.03 ng/mL. According to our review of the data, of 604 comparisons, both values were at or below the cutoff in 274 cases. Both were above the cutoff in 275 cases. In 2 cases, the value was above the cutoff when measured at the lower temperature but at or below the cutoff at the high temperature. In 53 cases, the measurement was at or below the cutoff when measured at the lower temperature but above the cutoff at the high temperature. The proportion of observations above 0.03 ng/mL varied by temperature as follows:

temp	18°C	22°C	26°C
% above cutoff	46.4 (51/110)	47.6 (39/82)	55.5 (61/110)
temp	20°C	24°C	28°C
% above cutoff	42.7 (47/110)	48.1 (53/110)	57.3 (63/110)

In the case of nearly all discrepancies, a sample was negative at the lower temperature and positive at the higher temperature. We performed further

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analysis using Passing-Bablok regression. The estimates of the intercepts in these regression was always 0, but, for example, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 with a 95% confidence interval of (1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 with a 95% confidence interval of (1.26, 1.40). Based on this analysis and the analysis provided in the table above, we have serious concerns that higher temperatures consistently yielded higher troponin measurements. Therefore, we do not believe that the data provided demonstrates concordance across temperatures.

ii. A p-value above 0.05 does not prove that there is no meaningful bias. A more appropriate acceptance criteria would require that the study prove that the level of disagreement between measures taken at different temperatures be statistically significantly below a pre-specified clinically acceptable level. Confidence intervals (accounting for repeated measures on individual subjects) should be provided for all measures of agreement.

b. Thermal Sensitivity-Robustness: This study used native plasma/serum, spiked plasma/serum and quality control materials at 10 different levels of troponin I, 2 instruments and 6 ambient temperature conditions. Each sample was tested in replicates of 5 on each instrument and at each temperature condition. A calibration curve was established at each temperature condition on each instrument. The individual results were calculated from the calibration curve established at each temperature. A percent difference in the average dose at each temperature compared to the mean dose achieved at 25°C was calculated for each sample and plotted as a function of temperature. Your acceptance criteria were that the slope term of each linear fit is either not significant or significant but has an average slope ≤ 0.010. Your results met your acceptance criteria since all slopes were significant but had an average slope ≤ 0.010. We do not know how to interpret this study since it was not performed as this device is intended to be used. While you claim that the instrument calibration is stable for 56 days (irrespective of ambient temperature), this study was performed by generating a calibration curve at each temperature tested. We are concerned that the test results obtained may be more accurate if the measurement is taken at the same temperature it was calibrated. Furthermore, we do not understand the rationale of your acceptance criteria. Therefore, we are concerned that this study design does not demonstrate that the thermal sensitivity issue has been resolved.

c. Thermal Sensitivity—Impact on Cross-Temperature Method Comparison: This study tested 108 lithium heparin plasma patient samples in replicates of 2 at each of 3 temperatures (18°C, 23°C and 28°C ± 2°C). The study was run on 2 instruments and 1 reagent lot. Individual sample results were calculated from the calibration curve established at each temperature. These 6 results where averaged to determine the best estimate for each sample at each temperature. Using this best estimate, between-temperature calculation using a Passing-Bablok regression were performed as follows: 23°C vs 18°C, 23°C vs 28°C and 28°C vs 18°C. Your acceptance criteria was that the slope should be 1.00 ± 0.10; $r \geq 0.95$. As discussed above in 1b, we do not know how to interpret this study since it was not performed as this device is intended to be used (i.e. generating calibration curves at each temperature is not the labeled procedure for this assay). We are also concerned that your proposed

acceptance criteria are too broad for the intent of this testing and ultimately that your study design does not demonstrate that the thermal sensitivity issue has been resolved.

d. We are concerned that the criteria of ± 2°C for your temperature studies may be too broad for your thermal sensitivity studies. We recommend that you tighten this criteria for any new studies you perform.

Based on the results of the "thermal sensitivity-impact on low dose concordance/agreement study, the LoQ studies (see item 5c below) and the linearity study (see item 6 below), we have serious concerns that you have not resolved the temperature sensitivity issue of your assay. We believe that the unresolved temperature sensitivity issue affects the safe use of this device on patients. In order to address this deficiency, you need to solve the temperature sensitivity issue. Once you have solved the temperature sensitivity issue, please address the following deficiencies. You should address them in any new studies you perform.

2. Intended Use: Your current intended use is "[t]he Access Accu TnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increase probability of ischemic events requiring urgent revascularization procedures." We have the following concerns/recommendations:
   a. You have not provided data from a clinical study demonstrating that this assay aids in the stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increase probability of ischemic events requiring urgent revascularization procedures. As we discussed under pre-IDE I100255, a risk prediction claim will require additional studies. Therefore, at this time, it seems that you do not have evidence to support a prognostic claim. We recommend that you remove the prognosis claim from your intended use statement.
   b. Since we are not sure that the matrix comparison studies provided demonstrate that the lithium heparin plasma test results and the serum test results are identical, you may not be able to support your claim that this device can be used on both serum and lithium heparin plasma samples (see item 4). Please amend your intended use if necessary.

3. Pivotal Clinical Trial: Please provide the following information regarding your clinical study:
   a. Poolability of investigation site data: Please address the following:
      i. On page 60, you examine whether AUC varies by site. Please explain what measurements were included in this analysis. That is, were all samples included? One sample per subject? You offer that you obtained a p-value of at least 0.19 but do not explain what hypothesis was tested. Please provide this hypothesis.

Without knowing what hypothesis was tested on what data, FDA cannot assess the validity of your finding.

ii. To further justify pooling by site for the efficacy analysis, please provide FDA with a calculation of the proportion of subjects with MI by site, with 95% confidence intervals. Please also provide estimates of sensitivity and specificity, by time from onset of symptoms, with 95% confidence intervals. Please perform the same analysis by time from hospital admission.

b. Diagnostic sensitivity and specificity by time after symptom onset: Please provide the following:

i. When a subject has more than 1 measurement <8 or ≥8 hours following the onset of symptoms, only 1 measurement is used in the analysis. How is it determined which measurement is included? Ideally, all available observations should be included in the analysis with adjustments made to account for the correlation between repeat measurements made on individual subjects. See Emir et al's 1998 paper in Statistics in Medicine "Analysis of repeated markers used to predict progression of cancer". Please discuss how your analysis reflects how this device will be used and how you will demonstrate the clinical performance of your device in an unbiased manner.

ii. Some clinicians may also want to see performance characteristic at < 12 hours and ≥ 12 hours after symptom onset. Please provide this analysis if available.

c. Diagnostic sensitivity and specificity by time after admission: Please address the following:

i. When a subject has more than 1 observation in a given interval, were all observations included or only 1? According to our review of your data there were at least 60 cases in which a subject had more than 1 draw in a given interval. If all were included, you should adjust the analysis to account for correlation between those observations. If only 1 was included, please explain how the measurement used in the analysis was chosen. Please discuss how your analysis reflects how this device will be used and how you will demonstrate the clinical performance of your device in an unbiased manner.

ii. According to the line data, all 1929 subjects have draws at time zero. There are 21 additional draws occurring between 0.1 and 0.9 hours after baseline. Are these 21 draws not included in the analyses? Are the 70 draws that occurred exactly 3 hours after baseline considered to be in the 1-3 or 3-6 bin? Similarly are the 38 draws that occurred at exactly 6 hours in the 3-6 hour bin or the 6-9 hour bin? There are another 70 draws taken more than 9 hours after baseline. Are these excluded from analyses?

d. Confidence interval analysis: Particularly for smaller samples and for estimates of proportions close to 1, the Wald confidence intervals offer less accurate results than exact confidence intervals. For example, the 95% CI for sensitivity at 6-9 hours is [77.9-97.4] using the exact method. This is noticeably lower than the [82.0-99.4] that you calculated using Wald. Please repeat and report your analysis using exact confidence intervals for all confidence intervals regarding proportions.

e. Inclusion criteria: You included patient presenting to the emergency room with chest pains occurring "at rest". What is your definition of "at rest"? Did you exclude patients presenting with chest pains following exercise or other stressful

situations? If so, please justify why the exclusion of these patients did not bias the results from your clinical study and why you believe these patients are not part of the intended use population of your device.

f. Instrument calibration: Please describe the frequency at which the testing laboratories calibrated each instruments while they were determining the troponin results for the pivotal clinical trial, the matrix comparison trial and the reference interval trial.

4. Matrix comparison study: You compared lithium heparin plasma and serum using native patient samples randomly selected from among the entire pivotal trial cohort. Lithium heparin plasma and serum results were determined on the Access 2 Instrument in singlet, using 3 lots of reagents. A total of 107 matched samples were included in this analysis. You provided Passing Bablok regression analysis for samples ranging from 0.01 to 20 ng/mL and for the subset of samples within the 107 samples that ranged from 0.01 to 5 ng/mL. The results are as follow:

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.01 – 20	107	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00
0.01 - 5	104	1.00 (1.00 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00

You concluded that excellent agreement was observed and that these results are similar to those reported in the analytical performance section. However, in the points to consider for Troponin 510(k) submission provided to you under pre-IDE I100255 we recommended that as part of your pivotal clinical study, you collect and test specimens for each claimed sample matrix to obtain clearance for multiple matrices. We still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) when serum samples are used at the pre-specified cut-offs.

5. Limits of detection: The limits of detection for the AccuTnI assay were assessed through a series of studies. However, most of these studies were not performed following the instructions in the package insert. Importantly, while you claim that the instrument calibration is stable for 56 days, many of these studies were performed by generating a calibration curve for each run or at each temperature tested. Therefore, we have the following concerns with your studies:

a. Limit of the blank (LoB): You performed a standardized LoB study and a multi temperature LoB study. However, a calibration curve was generated with each run for the standardized study and a calibration curve was generated with each run at each temperature for the multi temperature LoB study. Since both of these studies were not performed as the device is intended to be use, we cannot interpret your results. We do not believe that your study design supports the statement that the LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C. Please provide new LoB studies following the exact instructions in your package insert (particularly your calibration claim) to determine the LoB and to

support your claim that the LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.

b. Limit of detection (LoD): You performed 2 studies to determine the LoD of your assay. The standardized study was comprised of 12 runs on 3 instruments with 2 reagent lots and 2 calibrator lots per instrument at each of 3 ambient temperatures. A calibration curve was generated with each run. For the multi-temperature study, 5 lithium heparin plasma samples were tested in replicates of 3 for each of 12 runs on 3 instruments, 2 reagent lots and 2 calibrator lots at 18°C, 20°C, 22°C, 24°C, 26°C and 28°C (± 2°C for each temperature setting). A calibration curve was generated with each run at each temperature. Since neither of these studies was performed as this device is intended to be used, we do not know how to interpret your results (please see 1b for additional discussion regarding our concern with your calibration approach). Currently, your study design does not support the statement that the LoD is not affected by changes in ambient temperature across the operating range of 18°C to 28°C. You should repeat the LoD studies following the instructions in your package insert (particularly your calibration claim). Please also closely follow the recommendation in CLSI EP17 and provide the exact formula(s) used to determine the LoD.

c. Limit of quantitation (LoQ): You performed 2 different experiments to determine the LoQ of your device. The standardized LoQ study was performed using 7 lithium heparin plasma samples with low levels of troponin. Each sample was tested in replicates of 3 for each run. The study was performed on 3 instruments using 3 reagent lots at 18°C, 28°C and NLC (defined as normal laboratory conditions ranging from 21°C to 25°C). A single calibration curve was generated at each temperature. For the multi temperature study, 7 samples were prepared and each sample was tested in replicates of 3 for each run. A total of 24 runs were completed using 3 instruments, 2 reagent lots and 2 calibrator lots. A single calibration curve was generated at 24°C for this study. Because of the different calibration approaches, your experiments are difficult to interpret (see 1b). From the precision profile you determined the concentrations corresponding to a 10% and 20% total CV by interpolation. We do not concur with determining the LoQ based on interpolation of your data. According to our review of your data, from the standardized LoQ study, at 18°C the lowest value with a CV less than 10% is 0.026 ng/mL, at NLC it is 0.030 ng/mL and at 28°C it is 0.044 ng/mL. Therefore, according to this data, your LoQ is 0.044 at 10% CV (and 0.029 ng/mL for a CV less than 20%). Meanwhile, for the multi-temperature LoQ precision results the lowest value with a CV less than 20% and 10% is 0.027. Therefore your studies do not support your claim that the LoQ is 0.03 ng/mL at 10% CV and 0.01 ng/mL at 20% CV. Furthermore, we are very concerned that your LoQ seems to differ depending on the temperature (i.e. 0.044 ng/mL at 28°C, 0.030 ng/mL at NLC and 0.026 ng/mL at 18°C). We have serious concerns that you have not resolved the thermal sensitivity issue since the LoQ of your device seems to depend on the ambient temperature (please refer to item 1). Once you have resolved your temperature sensitivity issue, please provide new LoQ studies following the exact instructions in your package insert (particularly your calibration claim) to determine the LoQ for your device and to support your claim

that the LoQ is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.

d. Please clarify if the patient samples for the LoD and LoQ studies are spiked with exogenous troponin or if the patient samples are all natural, unmodified patient samples. We recommend that for your new LoD and LoQ studies, you should use natural, unmodified patient samples to determine your claims.
e. Please also address the item listed in 1d.

6. Linearity: You performed 12 standardized studies to evaluate the linearity of your device. Four studies were performed at 18°C, 28°C and NLC (21°C to 25°C) using 2 lots or reagents and 2 instruments. You used a synthetic matrix (buffered bovine serum albumin) for your samples. The results of your linearity studies are summarized in the following table:

Temp	Reagent	Instrument	Slope	intercept
18°C	116677	501007	0.8755	0.0014
18°C	116677	502884	0.8467	0.0002
18°C	116678	501007	0.8593	0.0000
18°C	116678	502884	0.8263	0.0000
NLC	116677	500616	0.9513	0.0005
NLC	116677	507310	0.9137	0.0008
NLC	116678	500616	0.9367	0.0003
NLC	116678	507310	0.9103	0.0007
28°C	116677	501007	1.127	0.0010
28°C	116677	502884	1.053	0.0004
28°C	116678	501007	1.122	0.0014
28°C	116678	502884	1.043	0.0003

Your acceptance criteria are that the higher order (2nd and 3rd) term of the polynomial fit must be non-significant. If it is significant, the fit of the polynomial regression demonstrating significance must have a bias at each sample tested of ≤ 16% for doses > 0.105 ng/mL or ≤ 0.0168 ng/mL for doses ≤ 0.105 ng/mL. Based on these results, you concluded that "all reagent pack lot and instrument combinations met the acceptance criteria for linearity at the 3 ambient temperature conditions tested and demonstrates linearity across the measuring range". We do not concur with your conclusion. Specifically:

a. Based on your data, the linearity varies depending on the temperature. Specifically: At 18°C, the slope of your experiments range from 0.8263 to 0.8755, at NLC, the slopes range from 0.9103 to 0.9513 and at 28°C, the slopes range from 1.053 to 1.127 demonstrating differences in the performance of this assay depending on the temperature. We have serious concerns that you have not resolved the thermal sensitivity issue and the test results obtained using your device can differ depending on the ambient temperature (please refer to item 1).
b. Furthermore, as we discussed under pre-IDE I100255/S002, we are concerned that your acceptance criteria are too broad for the intent of this testing. Once you resolve the temperature sensitivity issue, please perform new linearity studies. We

recommend that you tighten your acceptance criteria based on the medical needs of your proposed device.

c. Since we do not know if a synthetic matrix will mimic the performance of your device on patient samples, we recommend that you perform the studies using intended use patient samples (e.g. lithium heparin patient samples).
d. Please also address the item listed in 1d.

7. Field Effectiveness Study: You performed internal and external "Field Effectiveness" studies to assess the precision of the AccuTnI assay when used with the thermal algorithm on the Access 2 instruments. We have the following concerns with your studies:
   a. For the internal study, you used 5 cTnI commercial controls. The ambient temperature of the lab cycled (from 18°C to 28 °C) to reflect the worst case thermal profile for Access AccuTnI customers. The acceptance criterion is defined as the variance of the thermal-algorithm-adjusted results for each sample on each instrument must be less than or equal to the unadjusted results. Precision of the thermal algorithm adjusted results for the samples on each instrument must be ≤ 8% CV for concentration > 0.105 ng/mL and ≤ 0.0084 ng/mL standard deviation for concentrations ≤ 0.105 ng/mL.
      i. We are concerned that your acceptance criteria for normal troponin values and values around the medical decision point may be too broad. We recommend that you tighten these criteria based on the medical needs of this assay and also include acceptance criteria for temperature bias.
      ii. We also recommend that you include several natural patient samples in your field effectiveness studies.
   b. For the external study, you used 5 external sites that performed a multi-day precision study on Access 2 instruments using tri-level commercial quality control samples from 2 sources. Your acceptance criteria is that the variance of the adjusted results for each sample greater than the 10% CV LoQ acceptance criteria of 0.06 ng/mL must be less than or equal to the unadjusted results. Precision of the thermal algorithm adjusted results for the samples on each instrument must be ≤ 8% CV for concentration > 0.105 ng/mL and ≤ 0.0084 ng/mL standard deviation for concentrations ≤ 0.105 ng/mL.
      i. It seems that you did not monitor the temperature changes (if any) that occurred during this testing. In order for this field testing to demonstrate that the solution to your thermal sensitivity issue is valid, you should make sure that temperature changes (encompassing your ambient temperature claim) occur during the course of the study and that those temperature changes are documented.
      ii. We are also concerned that your acceptance criteria for normal troponin values and values around the medical decision point may be too broad. We recommend that you tighten these criteria based on the medical needs of this assay and also include acceptance criteria for temperature bias.
      iii. We also recommend that you include several unmodified natural patient samples in your field effectiveness studies.

8. Interference: We have the following concerns with your study:

a. You investigated potential interfering substances at 18°C, 28°C and NLC (21°C to 25°C) using 2 levels of interferent added to lithium heparin plasma pools containing ≤ 0.01ng/mL and 0.5 ng/mL troponin samples. Non interference was defined for troponin values > 0.105 ng/mL as a percent change ≤ 10.0%. For normal samples, either the test sample must read less than or equal to the established 99th percentile URL (0.02); or, if the test samples exceed the established 99th percentile URL, the difference between the test and the control sample must be ≤ 0.01 ng/mL. We are concerned that since the lower concentration of troponin tested is below your LoQ, your results are difficult to interpret. Specifically, several individual replicates in the studies have higher troponin values than other replicates (which tend to have troponin values between 0 and 0.01 ng/mL). The following table lists the individual replicates:

Compound	Temperature	Treatment group	Replicate	Troponin result ng/mL
CTS Auto-gloss	NLC	CLS	10	0.0249
Triglyceride-Intralipid	NLC	CLP	1	0.1633
Hemoglobin	NLC	TLP	7	0.0253
Trimethoprim	NLC	CLP	10	0.0260
Phenytoin	NLC	TLP	5	0.8676
	NLC	TLP	8	0.0436
Acetaminophen	NLC	CLS	7	0.0670
Simvastatin	28°C	TLS	9 and 10	0.035
Cinnarizine	28°C	CLS	7	0.028
Heparin-Sodium	28°C	CLP	4	0.051
Human serum albumin	28°C	CLP	4	0.023
	28°C	CLP	5 and 8	0.022

Furthermore, our review of your data indicates that phenytoin at 10 mg/dL at NLC significantly interfered with the performance of your assay since the mean of the treated group is 0.0915 (above the 99th percentile URL) and the untreated samples have a mean of 0. We recommend that you perform additional interference studies with a low troponin sample that is closer to the cut-off of your assay and above your LoQ in order to substantiate your interference claims.

b. We are also concerned that the acceptance criteria for the normal samples are too broad (according to our understanding, the allowable difference can be up to 50%). You should tighten your criteria when evaluating your new studies based on the medical needs of your assay.

c. Furthermore, we are concerned that your sodium heparin interference claim could be misinterpreted by the end users as an anticoagulant claim. Since interference studies are not sufficient to claim a specific anticoagulant, we recommend that you remove sodium heparin from your interference claim.

d. We recommend that you test a higher concentration of triglycerides. Your predicate device tested 1000 mg/dL triglycerides while you tested 500 mg/dL. Please provide data evaluating at least 1000 mg/dL triglycerides on the performance of your device.

e. Please provide the rationale for the concentrations you tested for ambroxol, biotin, cinnarizine, cocaine, fibrinogen, Low MW heparin, nystatin, oxytetracycline and simvastatin (i.e. are these therapeutic/endogenous or elevated or toxic?) Please see section 5.5 "Interferent Test Concentrations" in "Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition" for recommendations on appropriate test concentrations. If necessary, please provide data from testing at additional concentrations of these potential interfering compounds.
f. Please explain what CTS Auto-gloss is and why you evaluated this compound as a potential interferent.
g. Please also address the item listed in 1d.

9. Cross reactivity: You investigated potential cross reactivity at 18°C, 28°C and NLC (21°C to 25°C). Potential cross-reactive substances were added to plasma pools at 2 concentrations of cTnI (≤ 0.01ng/mL and approximately 0.5 ng/mL troponin). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. You concluded that all percent cross reactivity is less than 1.00%. We are not sure we understand your study and conclusions. Specifically, CKMB and recombinant human troponin T seem to have significantly cross reacted with the assay (please see the table summarizing our review of your data):

Compound	Concentration tested	Temperature	Mean of control	Mean of treated
CKMB	1000 mg/dL	18°C	0.001	1.044
			0.673	1.805
		NLC	0	0.704
			0.654	1.411
		28°C	0	0.583
			0.657	1.292
Recombinant human troponin T	1000 mg/dL	18°C	0.008	0.128
		NLC	0.002	0.136
		28°C	0.002	0.133

While we understand that you evaluated very high concentrations of these compounds, the data provided do not substantiate your claim that the compounds you evaluated did not cross react with the assay. Therefore, please provide additional cross reactivity studies identifying the lowest level of each compound that did not cross-react with the performance of your assay. We recommend that you perform your new studies with a low troponin sample that is closer to the cut-off of your assay and above your LoQ in order to substantiate your cross reactivity claims.
e. Please also address the item listed in 1d.

10. Precision: The precision of the AccuTnI assay was assessed through a series of studies. The first studies are standardized total precision studies performed at 18°C, 28°C and NLC (21°C to 25°C). The standardized studies at 18°C and 28°C were performed internally while the NLC study was performed externally. One instrument and 1 reagent

lot was used per study. A single calibration curve was generated at each temperature for each study. A multi-temperature study was also conducted over 14 days, 48 runs at 18°C, 20°C, 22°C, 24°C, 26°C and 28°C (± 2°C for each temperature setting). One reagent lot and 1 instrument were used for this study. A single calibration curve was generated at 24 °C ± 2°C. The standardized studies and the multi-temperature study both used 3 commercial controls, 1 recombinant cTNI-spiked lithium heparin plasma sample and 1 pooled lithium heparin plasma sample. We are concerned that your precision studies may underestimate the imprecision of your assay. Specifically, the multi-temperature study used only 1 instrument and 1 reagent lot. Meanwhile, the standardized study design does not reflect the intended use of this device since the calibration strategy does not reflect the labeled instructions for the assay (see 1b for additional discussion). We recommend that you repeat your precision studies to closely reflect how the end user will utilize this device. We recommend that you include multiple reagent lots, multiple instruments and multiple temperatures closely following the labeled instructions of your assay. You should also include a natural (unmodified) low-level patient sample with troponin values close to your cut-offs in order to determine the imprecision of your device on natural patient samples at the medical decision points. Please also address the issue identified in 1d.

11. HAMA/Heterophile antibody interference studies: You performed testing using a control reagent pack with the conjugate formulation containing blockers and a test reagent pack where the formulation did not contain blockers using 45 suspected HAMA or heterophile samples. The relative light unit output and doses were compared for the suspected HAMA/heterophile interferent samples from both the test and control pack. Your acceptance criterion is defined as "this study is intended to characterize blocker effectiveness". You conclude that all samples with insignificant, moderate and high reactivity were effectively suppressed by the blocking agents. We are not sure we understand your study. Specifically, you do not seem to have a predetermined performance goal to define no interference. Therefore, please provide a summary table of the doses obtained with the control and test reagents. Please also clearly define the performance goal that you pre-defined as demonstrating no interference from HAMA/heterophile antibodies and provide evidence that you have met your pre-determined performance goals.

12. Analytical Matrix Comparison Studies: Please explain what features of the data led you to choose Passing-Bablok as opposed to, for example, Deming regression. How does the imprecision differ between the 2 matrices? Please also address the item listed in 1d.

13. Algorithm: You have not provided detailed information about the algorithm you developed to resolve the ambient temperature sensitivity issue. Therefore, please provide more information about your algorithm. Please describe the algorithm, how it works and please discuss how the algorithm was developed.

14. DxI Intrument: The purpose of Appendix 5 is described as "this document contains generalized requirements for thermal monitoring on both Access 2 and DxI." Appendix 10 also discuses software requirements for the DxI instrument. Meanwhile Appendix 13

page 5 states "since this implementation was done on DxI originally and fully verified before being merged to Access 2, only performing regression unit tests." On page 8 of Appendix 13 you state "run regression tests on merged code from DxI". Appendix 14, page 33 also lists "[m]erge calibration and result temperature calculation from DxI." On page 94 of appendix 14 you list "merged from DxI: Load new APF thermal data." On page 103 of appendix 14 you list "merge AP XML schema definition (XSD) file from DxI branch." On page 120 of appendix 14 you list "merge thermal correction database updates from DxI to Access 2 XP." We have the following recommendation and comment:

a. All software verification and validation activities should be fully performed on the Access 2 instrument in order to market this instrument with this software.
b. In the current submission, we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay System.

15. Additional software: Appendix 7, 8, 9 and 10 discuss the NexStep configuration. This is described as a "configuration of Access instruments that allows the laboratory to network several Access instruments together to manage the instrument data, both results, supplies and setup information from one PC." Please be advised that in the current submission we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay Systems using Access 2 3.3 software.

16. IUO and IVD builds. On page 9 of Appendix 15 you state that selected Access 2 test procedures will be verified on the IVD version. The IVD version contains changes to update Help and language string files. The IVD systems software CD also has the ability to auto detect the operating system on which the software is being installed and automatically installs the correct package for the targeted operating system. Please note that you should verify and validate the exact IVD software version that you intend to market. If you used the IUD software version in any of the clinical studies (reference interval trial, pivotal efficacy trial and matrix comparison trial), please justify why you believe validating the IUD software version also validates the clinical performance of the IVD software.

17. Hardware: On page 7-2 you state "The case temperature sensor (thermistor) is the critical hardware component used to detect small changes in temperature, and has an accuracy specification of ± 0.2°C. This specification of ± 0.2°C was 100% verified by the supplier. Manufacturing release procedures for new instruments ensure that verified thermistors are installed." You will need to ensure that all instruments running this assay have the verified thermistors installed.

18. Stability studies: Five studies were conducted to assess the stability of the Access AccuTnI reagent and calibration materials. We have the following concerns and recommendations:

a. Reagent pack real time stability: For the reagent pack real time stability, at each time point the mean value of each control was calculated. From this mean value a "Z" value was calculated as follows: Z = (observed dose-stated dose)/expected SD. You base your acceptance criteria on the Z value. For normal patient samples, all

values must be ≤ 0.04 ng/mL. We do not understand why the Z value is used as the acceptance criteria. Please explain the significance of the Z value and why it is appropriate to demonstrate acceptable stability for the control samples. We also do not understand why normal patient samples should all be ≤ 0.04 ng/mL. It seems that normal patient samples should be less than the established 99th percentile of the normal population. Therefore, we have the following recommendations:

i. We recommend that you add acceptance criteria for the precision and accuracy of each control sample at each time-point compared to time-point 0. Please keep in mind that since calculating means can potentially mask big differences in the performance of individual replicates, we do not believe that acceptable stability should be based on means. All replicates should fall within your pre-determined acceptance criteria.

ii. Please make sure that you base your new acceptance criteria on the medical needs of this assay.

b. Reagent Open Pack Stability: In order to determine acceptable open pack stability, mean doses for each sample at each time point were calculated. For samples ≤ 0.105 ng/mL, doses were scaled according to ± 125% of the expected SD to allow all data to be combined for analysis. Mean doses were plotted versus time and compared to baseline values. The best fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. As discussed above, we do not concur with acceptance criteria based on mean. Furthermore we do not concur with scaling doses according to the expected SD. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

c. Stored Calibration Curve Stability: In order to verify the 56 day stability of the stored calibration curve, mean doses for each sample at each time point were calculated. For samples ≤ 0.105 ng/mL, doses were scaled according to ± 125% of the expected SD. Mean doses were plotted versus time and compared to baseline values. The best fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. As discussed above, we do not concur with acceptance criteria based on mean and we do not concur with scaling doses according to the expected SD. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

d. Calibrator Real Time Stability: To determine the real time stability of the calibrators, the mean value of each control was calculate and the Z value was calculated as described above in "a". You base your acceptance criteria for controls on the Z value. For normal patient samples, all values must be ≤ 0.04 ng/mL. As discussed above in "a), it seems that normal patient samples should be less than the established 99th percentile of the normal population. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

e. Calibrator open vial stability: For the calibrator open vial stability, you propose to scale samples with doses ≤ 0.105 ng/mL to ± 125% of the expected SD and plot the mean doses of all controls versus time compared to baseline values. The best fit linear equation will be calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within

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± 10% from baseline. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

19. Device calibrators: It seems that the calibrators for use with the device may not have been previously cleared. They may be cleared with this submission. If this is the case, according to our guidance document on calibrators found at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092801.pdf you should provide a complete and detailed description of the protocol and procedures for the value assignment process and the validation process for the calibrators (see Section IV b-e of the guidance on calibrators referenced above). Furthermore, please specify what controls and calibrators were used during the value assignment procedure. Please describe how the assigned values were verified to be accurate. Independent controls should be included with each value determination run in order to validate the results. Please also describe the traceability of your calibrators.

20. Labeling: In addition to the labeling changes requested in the items above, please address the following. Please send updated labeling with your response.
    a. Clinical Sensitivity and Specificity. Please remove all data obtained using cut-offs that were not pre-specified. You should only provide clinical performance data for your pre-specified cut-offs (e.g. 0.02 and 0.03). You should also include the PPV and NPV of your assay at the different time points and at the different hours after symptom onset in the labeling.
    b. Please remove the information about Risk Stratification for NSTEMI/UA Patients. Please refer to 19a for additional discussion.
    c. We recommend that you remove the "method comparison" information from the labeling. As discussed in the points to consider for Troponin 510(k) submissions provided to you under pre-IDE I100255, a method comparison study that evaluates your test compared to a predicate device is not necessary. It is also not necessary to use the predicate device in your clinical study. We will review the cleared clinical performance of your predicate device to your clinical performance to determine whether your device is substantially equivalent. We are also concerned that the method comparison data is not clinically useful.

21. Please submit a new 510(k) summary with your response.

Reviewer Name and Signature:

Paula Caposino

Paula Velasco Caposino, Ph.D.
FDA/CDRH/OIVD/DCTD

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* * * COMMUNICATION RESULT REPORT (JUN. 21. 2012 1:20PM) * * *

FAX HEADER 1:
FAX HEADER 2:

TRANSMITTED/STORED : JUN. 21. 2012 12:50PM

MODE	OPTION	ADDRESS	RESULT	PAGE
6766 MEMORY TX		919523687610	OK	16/16

REASON FOR ERROR
E-1) HANG UP OR LINE FAIL
E-2) BUSY
E-3) NO ANSWER
E-4) NO FACSIMILE CONNECTION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

10903 New Hampshire Avenue
Silver Spring, MD 20993

Beckman Coulter, Inc.
c/o Valynda Machen, CQA, RAC
Group Manager, Regulatory Affairs
1000 Lake Hazeltine Drive
Chaska MN 55318

JUN 20 2012

Re: k121214
Trade Name: Access AccuTnI on the Access 2 Immunoassay Systems
Dated: April 20, 2012
Received: April 23, 2012

Dear Valynda Machen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a legally marketed predicate device based solely on the information you provided. To complete the review of your submission, we require the following information:

1. Thermal Sensitivity: You performed 3 studies to assess the effect of ambient temperature on the AccuTnI assay performance. We have the following concerns with your studies:
   a. Thermal Sensitivity-Impact on Low Dose Concordance/Agreement: Two hundred twenty lithium heparin plasma samples near the clinical cutoff were tested using 2 reagent lots on 2 instruments at 18, 20, 22, 24, 26 and 28°C ± 2°C. Each sample was divided into 3 aliquots and tested at either 18, 22 and 26°C or 20, 24 and 28°C. At each temperature, each sample was run in replicates of 2. A McNemar analysis was performed to determine whether the number of mismatched comparisons was due to random scatter or a systematic difference. In addition, bias between low and high temperature was computed using a log-log regression fit. Your acceptance criteria were that the McNemar p-value must be non-significant (≥0.05). If the p-value is significant, concordance must be ≥90%. Bias at the cutoffs must be ≤0.0084. Please address the following:
      i. You concluded that, in all comparisons of measurements taken on the same sample at different temperatures (averaging the duplicates taken for each measurement), there was agreement in 91% of the cases in terms of whether the values fell >0.03 or ≤0.03 ng/mL. According to our review of the data, of 604 comparisons, both values were at or below the cutoff in 274 cases. Both were above the cutoff in 275 cases. In 2 cases, the value was above the cutoff when measured at the lower temperature but at or below the cutoff at the high temperature. In 53 cases, the measurement was at or below the cutoff when measured at the lower temperature but above the cutoff at the high temperature. The proportion of observations above 0.03 ng/mL varied by temperature as follows:

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      i. You concluded that, in all comparisons of measurements taken on the same sample at different temperatures (averaging the duplicates taken for each measurement), there was agreement in 91% of the cases in terms of whether the values fell >0.03 or ≤0.03 ng/mL. According to our review of the data, of 604 comparisons, both values were at or below the cutoff in 274 cases. Both were above the cutoff in 275 cases. In 2 cases, the value was above the cutoff when measured at the lower temperature but at or below the cutoff at the high temperature. In 53 cases, the measurement was at or below the cutoff when measured at the lower temperature but above the cutoff at the high temperature. The proportion of observations above 0.03 ng/mL varied by temperature as follows:

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temp	18°C	22°C	26°C
% above cutoff	46.4 (51/110)	47.6 (39/82)	55.5 (61/110)
temp	20°C	24°C	28°C
% above cutoff	42.7 (47/110)	48.1 (53/110)	57.3 (63/110)

In the case of nearly all discrepancies, a sample was negative at the lower temperature and positive at the higher temperature. We performed further analysis using Passing-Bablok regression. The estimates of the intercepts in these regression was always 0, but, for example, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 with a 95% confidence interval of (1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 with a 95% confidence interval of (1.26, 1.40). Based on this analysis and the analysis provided in the table above, we have serious concerns that higher temperatures consistently yielded higher troponin measurements. Therefore, we do not believe that the data provided demonstrates concordance across temperatures.

ii. A p-value above 0.05 does not prove that there is no meaningful bias. A more appropriate acceptance criteria would require that the study prove that the level of disagreement between measures taken at different temperatures be statistically significantly below a pre-specified clinically acceptable level. Confidence intervals (accounting for repeated measures on individual subjects) should be provided for all measures of agreement.

b. Thermal Sensitivity-Robustness: This study used native plasma/serum, spiked plasma/serum and quality control materials at 10 different levels of troponin I, 2 instruments and 6 ambient temperature conditions. Each sample was tested in replicates of 5 on each instrument and at each temperature condition. A calibration curve was established at each temperature condition on each instrument. The individual results were calculated from the calibration curve established at each temperature. A percent difference in the average dose at each temperature compared to the mean dose achieved at 25°C was calculated for each sample and plotted as a function of temperature. Your acceptance criteria were that the slope term of each linear fit is either not significant or significant but has an average slope ≤ 0.010. Your results met your acceptance criteria since all slopes were significant but had an average slope ≤ 0.010. We do not know how to interpret this study since it was not performed as this device is intended to be used. While you claim that the instrument calibration is stable for 56 days (irrespective of ambient temperature), this study was performed by generating a calibration curve at each temperature tested. We are concerned that the test results obtained may be more accurate if the measurement is taken at the same temperature it was calibrated. Furthermore, we do not understand the rationale of your acceptance criteria. Therefore, we are concerned that this study design does not demonstrate that the thermal sensitivity issue has been resolved.

c. Thermal Sensitivity—Impact on Cross-Temperature Method Comparison: This study tested 108 lithium heparin plasma patient samples in replicates of 2 at each of 3 temperatures (18°C, 23°C and 28°C ± 2°C). The study was run on 2

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instruments and 1 reagent lot. Individual sample results were calculated from the calibration curve established at each temperature. These 6 results where averaged to determine the best estimate for each sample at each temperature. Using this best estimate, between-temperature calculation using a Passing-Bablok regression were performed as follows: 23°C vs 18°C, 23°C vs 28°C and 28°C vs 18°C. Your acceptance criteria was that the slope should be 1.00 ± 0.10; $r \geq 0.95$. As discussed above in 1b, we do not know how to interpret this study since it was not performed as this device is intended to be used (i.e. generating calibration curves at each temperature is not the labeled procedure for this assay). We are also concerned that your proposed acceptance criteria are too broad for the intent of this testing and ultimately that your study design does not demonstrate that the thermal sensitivity issue has been resolved.

d. We are concerned that the criteria of ± 2°C for your temperature studies may be too broad for your thermal sensitivity studies. We recommend that you tighten this criteria for any new studies you perform.

Based on the results of the "thermal sensitivity-impact on low dose concordance/agreement study, the LoQ studies (see item 5c below) and the linearity study (see item 6 below), we have serious concerns that you have not resolved the temperature sensitivity issue of your assay. We believe that the unresolved temperature sensitivity issue affects the safe use of this device on patients. In order to address this deficiency, you need to solve the temperature sensitivity issue. Once you have solved the temperature sensitivity issue, please address the following deficiencies. You should address them in any new studies you perform.

2. Intended Use: Your current intended use is "[t]he Access Accu TnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increase probability of ischemic events requiring urgent revascularization procedures." We have the following concerns/recommendations:
   a. You have not provided data from a clinical study demonstrating that this assay aids in the stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increase probability of ischemic events requiring urgent revascularization procedures. As we discussed under pre-IDE I100255, a risk prediction claim will require additional studies. Therefore, at this time, it seems that you do not have evidence to support a prognostic claim. We recommend that you remove the prognosis claim from your intended use statement.
   b. Since we are not sure that the matrix comparison studies provided demonstrate that the lithium heparin plasma test results and the serum test results are identical, you may not be able to support your claim that this device can be used on both serum and lithium heparin plasma samples (see item 4). Please amend your intended use if necessary.

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3. Pivotal Clinical Trial: Please provide the following information regarding your clinical study:
   a. Poolability of investigation site data: Please address the following:
      i. On page 60, you examine whether AUC varies by site. Please explain what measurements were included in this analysis. That is, were all samples included? One sample per subject? You offer that you obtained a p-value of at least 0.19 but do not explain what hypothesis was tested. Please provide this hypothesis. Without knowing what hypothesis was tested on what data, FDA cannot assess the validity of your finding.
      ii. To further justify pooling by site for the efficacy analysis, please provide FDA with a calculation of the proportion of subjects with MI by site, with 95% confidence intervals. Please also provide estimates of sensitivity and specificity, by time from onset of symptoms, with 95% confidence intervals. Please perform the same analysis by time from hospital admission.
   b. Diagnostic sensitivity and specificity by time after symptom onset: Please provide the following:
      i. When a subject has more than 1 measurement <8 or ≥8 hours following the onset of symptoms, only 1 measurement is used in the analysis. How is it determined which measurement is included? Ideally, all available observations should be included in the analysis with adjustments made to account for the correlation between repeat measurements made on individual subjects. See Emir et al's 1998 paper in Statistics in Medicine "Analysis of repeated markers used to predict progression of cancer". Please discuss how your analysis reflects how this device will be used and how you will demonstrate the clinical performance of your device in an unbiased manner.
      ii. Some clinicians may also want to see performance characteristic at < 12 hours and ≥ 12 hours after symptom onset. Please provide this analysis if available.
   c. Diagnostic sensitivity and specificity by time after admission: Please address the following:
      i. When a subject has more than 1 observation in a given interval, were all observations included or only 1? According to our review of your data there were at least 60 cases in which a subject had more than 1 draw in a given interval. If all were included, you should adjust the analysis to account for correlation between those observations. If only 1 was included, please explain how the measurement used in the analysis was chosen. Please discuss how your analysis reflects how this device will be used and how you will demonstrate the clinical performance of your device in an unbiased manner.
      ii. According to the line data, all 1929 subjects have draws at time zero. There are 21 additional draws occurring between 0.1 and 0.9 hours after baseline. Are these 21 draws not included in the analyses? Are the 70 draws that occurred exactly 3 hours after baseline considered to be in the 1-3 or 3-6 bin? Similarly are the 38 draws that occurred at exactly 6 hours in the 3-6 hour bin or the 6-9 hour bin? There are another 70 draws taken more than 9 hours after baseline. Are these excluded from analyses?

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d. Confidence interval analysis: Particularly for smaller samples and for estimates of proportions close to 1, the Wald confidence intervals offer less accurate results than exact confidence intervals. For example, the 95% CI for sensitivity at 6-9 hours is [77.9-97.4] using the exact method. This is noticeably lower than the [82.0-99.4] that you calculated using Wald. Please repeat and report your analysis using exact confidence intervals for all confidence intervals regarding proportions.
e. Inclusion criteria: You included patient presenting to the emergency room with chest pains occurring "at rest". What is your definition of "at rest"? Did you exclude patients presenting with chest pains following exercise or other stressful situations? If so, please justify why the exclusion of these patients did not bias the results from your clinical study and why you believe these patients are not part of the intended use population of your device.
f. Instrument calibration: Please describe the frequency at which the testing laboratories calibrated each instruments while they were determining the troponin results for the pivotal clinical trial, the matrix comparison trial and the reference interval trial.

4. Matrix comparison study: You compared lithium heparin plasma and serum using native patient samples randomly selected from among the entire pivotal trial cohort. Lithium heparin plasma and serum results were determined on the Access 2 Instrument in singlet, using 3 lots of reagents. A total of 107 matched samples were included in this analysis. You provided Passing Bablok regression analysis for samples ranging from 0.01 to 20 ng/mL and for the subset of samples within the 107 samples that ranged from 0.01 to 5 ng/mL. The results are as follow:

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.01 – 20	107	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00
0.01 - 5	104	1.00 (1.00 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00

You concluded that excellent agreement was observed and that these results are similar to those reported in the analytical performance section. However, in the points to consider for Troponin 510(k) submission provided to you under pre-IDE I100255 we recommended that as part of your pivotal clinical study, you collect and test specimens for each claimed sample matrix to obtain clearance for multiple matrices. We still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) when serum samples are used at the pre-specified cut-offs.

5. Limits of detection: The limits of detection for the AccuTnI assay were assessed through a series of studies. However, most of these studies were not performed following the instructions in the package insert. Importantly, while you claim that the instrument calibration is stable for 56 days, many of these studies were performed by generating a calibration curve for each run or at each temperature tested. Therefore, we have the following concerns with your studies:

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a. Limit of the blank (LoB): You performed a standardized LoB study and a multi temperature LoB study. However, a calibration curve was generated with each run for the standardized study and a calibration curve was generated with each run at each temperature for the multi temperature LoB study. Since both of these studies were not performed as the device is intended to be use, we cannot interpret your results. We do not believe that your study design supports the statement that the LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C. Please provide new LoB studies following the exact instructions in your package insert (particularly your calibration claim) to determine the LoB and to support your claim that the LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.
b. Limit of detection (LoD): You performed 2 studies to determine the LoD of your assay. The standardized study was comprised of 12 runs on 3 instruments with 2 reagent lots and 2 calibrator lots per instrument at each of 3 ambient temperatures. A calibration curve was generated with each run. For the multi-temperature study, 5 lithium heparin plasma samples were tested in replicates of 3 for each of 12 runs on 3 instruments, 2 reagent lots and 2 calibrator lots at 18°C, 20°C, 22°C, 24°C, 26°C and 28°C (± 2°C for each temperature setting). A calibration curve was generated with each run at each temperature. Since neither of these studies was performed as this device is intended to be used, we do not know how to interpret your results (please see 1b for additional discussion regarding our concern with your calibration approach). Currently, your study design does not support the statement that the LoD is not affected by changes in ambient temperature across the operating range of 18°C to 28°C. You should repeat the LoD studies following the instructions in your package insert (particularly your calibration claim). Please also closely follow the recommendation in CLSI EP17 and provide the exact formula(s) used to determine the LoD.
c. Limit of quantitation (LoQ): You performed 2 different experiments to determine the LoQ of your device. The standardized LoQ study was performed using 7 lithium heparin plasma samples with low levels of troponin. Each sample was tested in replicates of 3 for each run. The study was performed on 3 instruments using 3 reagent lots at 18°C, 28°C and NLC (defined as normal laboratory conditions ranging from 21°C to 25°C). A single calibration curve was generated at each temperature. For the multi temperature study, 7 samples were prepared and each sample was tested in replicates of 3 for each run. A total of 24 runs were completed using 3 instruments, 2 reagent lots and 2 calibrator lots. A single calibration curve was generated at 24°C for this study. Because of the different calibration approaches, your experiments are difficult to interpret (see 1b). From the precision profile you determined the concentrations corresponding to a 10% and 20% total CV by interpolation. We do not concur with determining the LoQ based on interpolation of your data. According to our review of your data, from the standardized LoQ study, at 18°C the lowest value with a CV less than 10% is 0.026 ng/mL, at NLC it is 0.030 ng/mL and at 28°C it is 0.044 ng/mL. Therefore, according to this data, your LoQ is 0.044 at 10% CV (and 0.029 ng/mL for a CV less than 20%). Meanwhile, for the multi-temperature LoQ precision results the lowest value with a CV less than 20% and 10% is 0.027. Therefore your studies

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do not support your claim that the LoQ is 0.03 ng/mL at 10% CV and 0.01 ng/mL at 20% CV. Furthermore, we are very concerned that your LoQ seems to differ depending on the temperature (i.e. 0.044 ng/mL at 28°C, 0.030 ng/mL at NLC and 0.026 ng/mL at 18°C). We have serious concerns that you have not resolved the thermal sensitivity issue since the LoQ of your device seems to depend on the ambient temperature (please refer to item 1). Once you have resolved your temperature sensitivity issue, please provide new LoQ studies following the exact instructions in your package insert (particularly your calibration claim) to determine the LoQ for your device and to support your claim that the LoQ is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.

d. Please clarify if the patient samples for the LoD and LoQ studies are spiked with exogenous troponin or if the patient samples are all natural, unmodified patient samples. We recommend that for your new LoD and LoQ studies, you should use natural, unmodified patient samples to determine your claims.
e. Please also address the item listed in 1d.

6. Linearity: You performed 12 standardized studies to evaluate the linearity of your device. Four studies were performed at 18°C, 28°C and NLC (21°C to 25°C) using 2 lots or reagents and 2 instruments. You used a synthetic matrix (buffered bovine serum albumin) for your samples. The results of your linearity studies are summarized in the following table:

Temp	Reagent	Instrument	Slope	intercept
18°C	116677	501007	0.8755	0.0014
18°C	116677	502884	0.8467	0.0002
18°C	116678	501007	0.8593	0.0000
18°C	116678	502884	0.8263	0.0000
NLC	116677	500616	0.9513	0.0005
NLC	116677	507310	0.9137	0.0008
NLC	116678	500616	0.9367	0.0003
NLC	116678	507310	0.9103	0.0007
28°C	116677	501007	1.127	0.0010
28°C	116677	502884	1.053	0.0004
28°C	116678	501007	1.122	0.0014
28°C	116678	502884	1.043	0.0003

Your acceptance criteria are that the higher order (2nd and 3rd) term of the polynomial fit must be non-significant. If it is significant, the fit of the polynomial regression demonstrating significance must have a bias at each sample tested of ≤ 16% for doses > 0.105 ng/mL or ≤ 0.0168 ng/mL for doses ≤ 0.105 ng/mL. Based on these results, you concluded that "all reagent pack lot and instrument combinations met the acceptance criteria for linearity at the 3 ambient temperature conditions tested and demonstrates linearity across the measuring range". We do not concur with your conclusion. Specifically:

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a. Based on your data, the linearity varies depending on the temperature. Specifically: At 18°C, the slope of your experiments range from 0.8263 to 0.8755, at NLC, the slopes range from 0.9103 to 0.9513 and at 28°C, the slopes range from 1.053 to 1.127 demonstrating differences in the performance of this assay depending on the temperature. We have serious concerns that you have not resolved the thermal sensitivity issue and the test results obtained using your device can differ depending on the ambient temperature (please refer to item 1).
b. Furthermore, as we discussed under pre-IDE I100255/S002, we are concerned that your acceptance criteria are too broad for the intent of this testing. Once you resolve the temperature sensitivity issue, please perform new linearity studies. We recommend that you tighten your acceptance criteria based on the medical needs of your proposed device.
c. Since we do not know if a synthetic matrix will mimic the performance of your device on patient samples, we recommend that you perform the studies using intended use patient samples (e.g. lithium heparin patient samples).
d. Please also address the item listed in 1d.

7. Field Effectiveness Study: You performed internal and external "Field Effectiveness" studies to assess the precision of the AccuTnI assay when used with the thermal algorithm on the Access 2 instruments. We have the following concerns with your studies:
   a. For the internal study, you used 5 cTnI commercial controls. The ambient temperature of the lab cycled (from 18°C to 28 °C) to reflect the worst case thermal profile for Access AccuTnI customers. The acceptance criterion is defined as the variance of the thermal-algorithm-adjusted results for each sample on each instrument must be less than or equal to the unadjusted results. Precision of the thermal algorithm adjusted results for the samples on each instrument must be ≤ 8% CV for concentration > 0.105 ng/mL and ≤ 0.0084 ng/mL standard deviation for concentrations ≤ 0.105 ng/mL.
      i. We are concerned that your acceptance criteria for normal troponin values and values around the medical decision point may be too broad. We recommend that you tighten these criteria based on the medical needs of this assay and also include acceptance criteria for temperature bias.
      ii. We also recommend that you include several natural patient samples in your field effectiveness studies.
   b. For the external study, you used 5 external sites that performed a multi-day precision study on Access 2 instruments using tri-level commercial quality control samples from 2 sources. Your acceptance criteria is that the variance of the adjusted results for each sample greater than the 10% CV LoQ acceptance criteria of 0.06 ng/mL must be less than or equal to the unadjusted results. Precision of the thermal algorithm adjusted results for the samples on each instrument must be ≤ 8% CV for concentration > 0.105 ng/mL and ≤ 0.0084 ng/mL standard deviation for concentrations ≤ 0.105 ng/mL.
      i. It seems that you did not monitor the temperature changes (if any) that occurred during this testing. In order for this field testing to demonstrate that the solution to your thermal sensitivity issue is valid, you should make sure

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that temperature changes (encompassing your ambient temperature claim) occur during the course of the study and that those temperature changes are documented.

ii. We are also concerned that your acceptance criteria for normal troponin values and values around the medical decision point may be too broad. We recommend that you tighten these criteria based on the medical needs of this assay and also include acceptance criteria for temperature bias.

iii. We also recommend that you include several unmodified natural patient samples in your field effectiveness studies.

8. Interference: We have the following concerns with your study:

a. You investigated potential interfering substances at 18°C, 28°C and NLC (21°C to 25°C) using 2 levels of interferent added to lithium heparin plasma pools containing ≤ 0.01ng/mL and 0.5 ng/mL troponin samples. Non interference was defined for troponin values > 0.105 ng/mL as a percent change ≤ 10.0%. For normal samples, either the test sample must read less than or equal to the established 99th percentile URL (0.02); or, if the test samples exceed the established 99th percentile URL, the difference between the test and the control sample must be ≤ 0.01 ng/mL. We are concerned that since the lower concentration of troponin tested is below your LoQ, your results are difficult to interpret. Specifically, several individual replicates in the studies have higher troponin values than other replicates (which tend to have troponin values between 0 and 0.01 ng/mL). The following table lists the individual replicates:

Compound	Temperature	Treatment group	Replicate	Troponin result ng/mL
CTS Auto-gloss	NLC	CLS	10	0.0249
Triglyceride-Intralipid	NLC	CLP	1	0.1633
Hemoglobin	NLC	TLP	7	0.0253
Trimethoprim	NLC	CLP	10	0.0260
Phenytoin	NLC	TLP	5	0.8676
	NLC	TLP	8	0.0436
Acetaminophen	NLC	CLS	7	0.0670
Simvastatin	28°C	TLS	9 and 10	0.035
Cinnarizine	28°C	CLS	7	0.028
Heparin-Sodium	28°C	CLP	4	0.051
Human serum albumin	28°C	CLP	4	0.023
	28°C	CLP	5 and 8	0.022

Furthermore, our review of your data indicates that phenytoin at 10 mg/dL at NLC significantly interfered with the performance of your assay since the mean of the treated group is 0.0915 (above the 99th percentile URL) and the untreated samples have a mean of 0. We recommend that you perform additional interference studies with a low troponin sample that is closer to the cut-off of your assay and above your LoQ in order to substantiate your interference claims.

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b. We are also concerned that the acceptance criteria for the normal samples are too broad (according to our understanding, the allowable difference can be up to 50%). You should tighten your criteria when evaluating your new studies based on the medical needs of your assay.
c. Furthermore, we are concerned that your sodium heparin interference claim could be misinterpreted by the end users as an anticoagulant claim. Since interference studies are not sufficient to claim a specific anticoagulant, we recommend that you remove sodium heparin from your interference claim.
d. We recommend that you test a higher concentration of triglycerides. Your predicate device tested 1000 mg/dL triglycerides while you tested 500 mg/dL. Please provide data evaluating at least 1000 mg/dL triglycerides on the performance of your device.
e. Please provide the rationale for the concentrations you tested for ambroxol, biotin, cinnarizine, cocaine, fibrinogen, Low MW heparin, nystatin, oxytetracycline and simvastatin (i.e. are these therapeutic/endogenous or elevated or toxic?) Please see section 5.5 "Interferent Test Concentrations" in "Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition" for recommendations on appropriate test concentrations. If necessary, please provide data from testing at additional concentrations of these potential interfering compounds.
f. Please explain what CTS Auto-gloss is and why you evaluated this compound as a potential interferent.
g. Please also address the item listed in 1d.

9. Cross reactivity: You investigated potential cross reactivity at 18°C, 28°C and NLC (21°C to 25°C). Potential cross-reactive substances were added to plasma pools at 2 concentrations of cTnI (≤ 0.01ng/mL and approximately 0.5 ng/mL troponin). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. You concluded that all percent cross reactivity is less than 1.00%. We are not sure we understand your study and conclusions. Specifically, CKMB and recombinant human troponin T seem to have significantly cross reacted with the assay (please see the table summarizing our review of your data):

Compound	Concentration tested	Temperature	Mean of control	Mean of treated
CKMB	1000 mg/dL	18°C	0.001	1.044
			0.673	1.805
		NLC	0	0.704
			0.654	1.411
		28°C	0	0.583
			0.657	1.292
Recombinant human troponin T	1000 mg/dL	18°C	0.008	0.128
		NLC	0.002	0.136
		28°C	0.002	0.133

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While we understand that you evaluated very high concentrations of these compounds, the data provided do not substantiate your claim that the compounds you evaluated did not cross react with the assay. Therefore, please provide additional cross reactivity studies identifying the lowest level of each compound that did not cross-react with the performance of your assay. We recommend that you perform your new studies with a low troponin sample that is closer to the cut-off of your assay and above your LoQ in order to substantiate your cross reactivity claims.

e. Please also address the item listed in 1d.

10. Precision: The precision of the AccuTnI assay was assessed through a series of studies. The first studies are standardized total precision studies performed at 18°C, 28°C and NLC (21°C to 25°C). The standardized studies at 18°C and 28°C were performed internally while the NLC study was performed externally. One instrument and 1 reagent lot was used per study. A single calibration curve was generated at each temperature for each study. A multi-temperature study was also conducted over 14 days, 48 runs at 18°C, 20°C, 22°C, 24°C, 26°C and 28°C (± 2°C for each temperature setting). One reagent lot and 1 instrument were used for this study. A single calibration curve was generated at 24 °C ± 2°C. The standardized studies and the multi-temperature study both used 3 commercial controls, 1 recombinant cTNI-spiked lithium heparin plasma sample and 1 pooled lithium heparin plasma sample. We are concerned that your precision studies may underestimate the imprecision of your assay. Specifically, the multi-temperature study used only 1 instrument and 1 reagent lot. Meanwhile, the standardized study design does not reflect the intended use of this device since the calibration strategy does not reflect the labeled instructions for the assay (see 1b for additional discussion). We recommend that you repeat your precision studies to closely reflect how the end user will utilize this device. We recommend that you include multiple reagent lots, multiple instruments and multiple temperatures closely following the labeled instructions of your assay. You should also include a natural (unmodified) low-level patient sample with troponin values close to your cut-offs in order to determine the imprecision of your device on natural patient samples at the medical decision points. Please also address the issue identified in 1d.

11. HAMA/Heterophile antibody interference studies: You performed testing using a control reagent pack with the conjugate formulation containing blockers and a test reagent pack where the formulation did not contain blockers using 45 suspected HAMA or heterophile samples. The relative light unit output and doses were compared for the suspected HAMA/heterophile interferent samples from both the test and control pack. Your acceptance criterion is defined as "this study is intended to characterize blocker effectiveness". You conclude that all samples with insignificant, moderate and high reactivity were effectively suppressed by the blocking agents. We are not sure we understand your study. Specifically, you do not seem to have a predetermined performance goal to define no interference. Therefore, please provide a summary table of the doses obtained with the control and test reagents. Please also clearly define the performance goal that you pre-defined as demonstrating no

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interference from HAMA/heterophile antibodies and provide evidence that you have met your pre-determined performance goals.

12. Analytical Matrix Comparison Studies: Please explain what features of the data led you to choose Passing-Bablok as opposed to, for example, Deming regression. How does the imprecision differ between the 2 matrices? Please also address the item listed in 1d.

13. Algorithm: You have not provided detailed information about the algorithm you developed to resolve the ambient temperature sensitivity issue. Therefore, please provide more information about your algorithm. Please describe the algorithm, how it works and please discuss how the algorithm was developed.

14. DxI Intrument: The purpose of Appendix 5 is described as "this document contains generalized requirements for thermal monitoring on both Access 2 and DxI." Appendix 10 also discuses software requirements for the DxI instrument. Meanwhile Appendix 13 page 5 states "since this implementation was done on DxI originally and fully verified before being merged to Access 2, only performing regression unit tests." On page 8 of Appendix 13 you state "run regression tests on merged code from DxI". Appendix 14, page 33 also lists "[m]erge calibration and result temperature calculation from DxI." On page 94 of appendix 14 you list "merged from DxI: Load new APF thermal data." On page 103 of appendix 14 you list "merge AP XML schema definition (XSD) file from DxI branch." On page 120 of appendix 14 you list "merge thermal correction database updates from DxI to Access 2 XP." We have the following recommendation and comment:
    a. All software verification and validation activities should be fully performed on the Access 2 instrument in order to market this instrument with this software.
    b. In the current submission, we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay System.

15. Additional software: Appendix 7, 8, 9 and 10 discuss the NexStep configuration. This is described as a "configuration of Access instruments that allows the laboratory to network several Access instruments together to manage the instrument data, both results, supplies and setup information from one PC." Please be advised that in the current submission we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay Systems using Access 2 3.3 software.

16. IUO and IVD builds. On page 9 of Appendix 15 you state that selected Access 2 test procedures will be verified on the IVD version. The IVD version contains changes to update Help and language string files. The IVD systems software CD also has the ability to auto detect the operating system on which the software is being installed and automatically installs the correct package for the targeted operating system. Please note that you should verify and validate the exact IVD software version that you intend to market. If you used the IUD software version in any of the clinical studies (reference interval trial, pivotal efficacy trial and matrix comparison trial),

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please justify why you believe validating the IUD software version also validates the clinical performance of the IVD software.

17. Hardware: On page 7-2 you state "The case temperature sensor (thermistor) is the critical hardware component used to detect small changes in temperature, and has an accuracy specification of ± 0.2°C. This specification of ± 0.2°C was 100% verified by the supplier. Manufacturing release procedures for new instruments ensure that verified thermistors are installed." You will need to ensure that all instruments running this assay have the verified thermistors installed.

18. Stability studies: Five studies were conducted to assess the stability of the Access AccuTnI reagent and calibration materials. We have the following concerns and recommendations:
    a. Reagent pack real time stability: For the reagent pack real time stability, at each time point the mean value of each control was calculated. From this mean value a "Z" value was calculated as follows: Z = (observed dose-stated dose)/expected SD. You base your acceptance criteria on the Z value. For normal patient samples, all values must be ≤ 0.04 ng/mL. We do not understand why the Z value is used as the acceptance criteria. Please explain the significance of the Z value and why it is appropriate to demonstrate acceptable stability for the control samples. We also do not understand why normal patient samples should all be ≤ 0.04 ng/mL. It seems that normal patient samples should be less than the established 99th percentile of the normal population. Therefore, we have the following recommendations:
        i. We recommend that you add acceptance criteria for the precision and accuracy of each control sample at each time-point compared to time-point 0. Please keep in mind that since calculating means can potentially mask big differences in the performance of individual replicates, we do not believe that acceptable stability should be based on means. All replicates should fall within your pre-determined acceptance criteria.
        ii. Please make sure that you base your new acceptance criteria on the medical needs of this assay.
    b. Reagent Open Pack Stability: In order to determine acceptable open pack stability, mean doses for each sample at each time point were calculated. For samples ≤ 0.105 ng/mL, doses were scaled according to ± 125% of the expected SD to allow all data to be combined for analysis. Mean doses were plotted versus time and compared to baseline values. The best fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. As discussed above, we do not concur with acceptance criteria based on mean. Furthermore we do not concur with scaling doses according to the expected SD. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.
    c. Stored Calibration Curve Stability: In order to verify the 56 day stability of the stored calibration curve, mean doses for each sample at each time point were calculated. For samples ≤ 0.105 ng/mL, doses were scaled according to ± 125%

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of the expected SD. Mean doses were plotted versus time and compared to baseline values. The best fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. As discussed above, we do not concur with acceptance criteria based on mean and we do not concur with scaling doses according to the expected SD. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

d. Calibrator Real Time Stability: To determine the real time stability of the calibrators, the mean value of each control was calculate and the Z value was calculated as described above in "a". You base your acceptance criteria for controls on the Z value. For normal patient samples, all values must be ≤ 0.04 ng/mL. As discussed above in "a), it seems that normal patient samples should be less than the established 99th percentile of the normal population. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.
e. Calibrator open vial stability: For the calibrator open vial stability, you propose to scale samples with doses ≤ 0.105 ng/mL to ± 125% of the expected SD and plot the mean doses of all controls versus time compared to baseline values. The best fit linear equation will be calculated to estimate the percent dose change with 95% confidence intervals. Your acceptance criterion is that the fitted line must be within ± 10% from baseline. Please refer to item 18ai and 18aii above for our recommendations for your stability studies.

19. Device calibrators: It seems that the calibrators for use with the device may not have been previously cleared. They may be cleared with this submission. If this is the case, according to our guidance document on calibrators found at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092801.pdf you should provide a complete and detailed description of the protocol and procedures for the value assignment process and the validation process for the calibrators (see Section IV b-e of the guidance on calibrators referenced above). Furthermore, please specify what controls and calibrators were used during the value assignment procedure. Please describe how the assigned values were verified to be accurate. Independent controls should be included with each value determination run in order to validate the results. Please also describe the traceability of your calibrators.

20. Labeling: In addition to the labeling changes requested in the items above, please address the following. Please send updated labeling with your response.
    a. Clinical Sensitivity and Specificity. Please remove all data obtained using cut-offs that were not pre-specified. You should only provide clinical performance data for your pre-specified cut-offs (e.g. 0.02 and 0.03). You should also include the PPV and NPV of your assay at the different time points and at the different hours after symptom onset in the labeling.
    b. Please remove the information about Risk Stratification for NSTEMI/UA Patients. Please refer to 19a for additional discussion.
    c. We recommend that you remove the "method comparison" information from the labeling. As discussed in the points to consider for Troponin 510(k) submissions

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provided to you under pre-IDE I100255, a method comparison study that evaluates your test compared to a predicate device is not necessary. It is also not necessary to use the predicate device in your clinical study. We will review the cleared clinical performance of your predicate device to your clinical performance to determine whether your device is substantially equivalent. We are also concerned that the method comparison data is not clinically useful.

21. Please submit a new 510(k) summary with your response.

Once we receive your response to the above deficiencies regarding your 510(k) submission, please be advised that there may be additional issues that arise after further review of your submission.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act (Act) for determining substantial equivalence of your device.

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Act. You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations (21 CFR 812).

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k)(21 CFR 807.87(l)); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. For guidance on 510(k) actions, please see our guidance document entitled, "Guidance for Industry and FDA Staff: Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements" at www.fda.gov/cdrh/ode/guidance/1655.html.

If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the additional information request.

The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. You may review this document at http://www.fda.gov/cdrh/mdufma/guidance/1219.html.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

Food and Drug Administration
Center for Devices and
Radiological Health
Document Mail Center – WO66 - G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

If you have any questions concerning the contents of the letter, please contact Paula Velasco Caposino at (301) 796-6160. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or at (301) 796-7100, or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

for

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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cc: DMC – 510(k) Staff
OIVD Reviewer – Paula Velasco Caposino (DCTD)
D.O.

Div/Branch	Last Name	Date	Div/Branch	Last Name	Date
OIVD/DCTD	CAPOSINO	6/20/12			
OIVD (DCTD	Qin	6/20/12			

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Paula V. Caposino

Subject: 510(k) Number K121214

To: The Record

Please list CTS decision code AI

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☒ Hold (Additional Information or Telephone Hold).

☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	✓	
510(k) Summary /510(k) Statement	*Attach Summary*	✓	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	✓	
Is the device Class III?			
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)?			
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank? (If study was			

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conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)

Does this device include an Animal Tissue Source?

All Pediatric Patients age<=21

Neonate/Newborn (Birth to 28 days)

Infant (29 days -< 2 years old)

Child (2 years -< 12 years old)

Adolescent (12 years -< 18 years old)

Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)

Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)

Nanotechnology

Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html) *Contact OC.*

Regulation Number **Class*** **Product Code**

(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: (Branch Chief) DCTD (Branch Code) 6/20/12 (Date)

Final Review: (Division Director) (Date)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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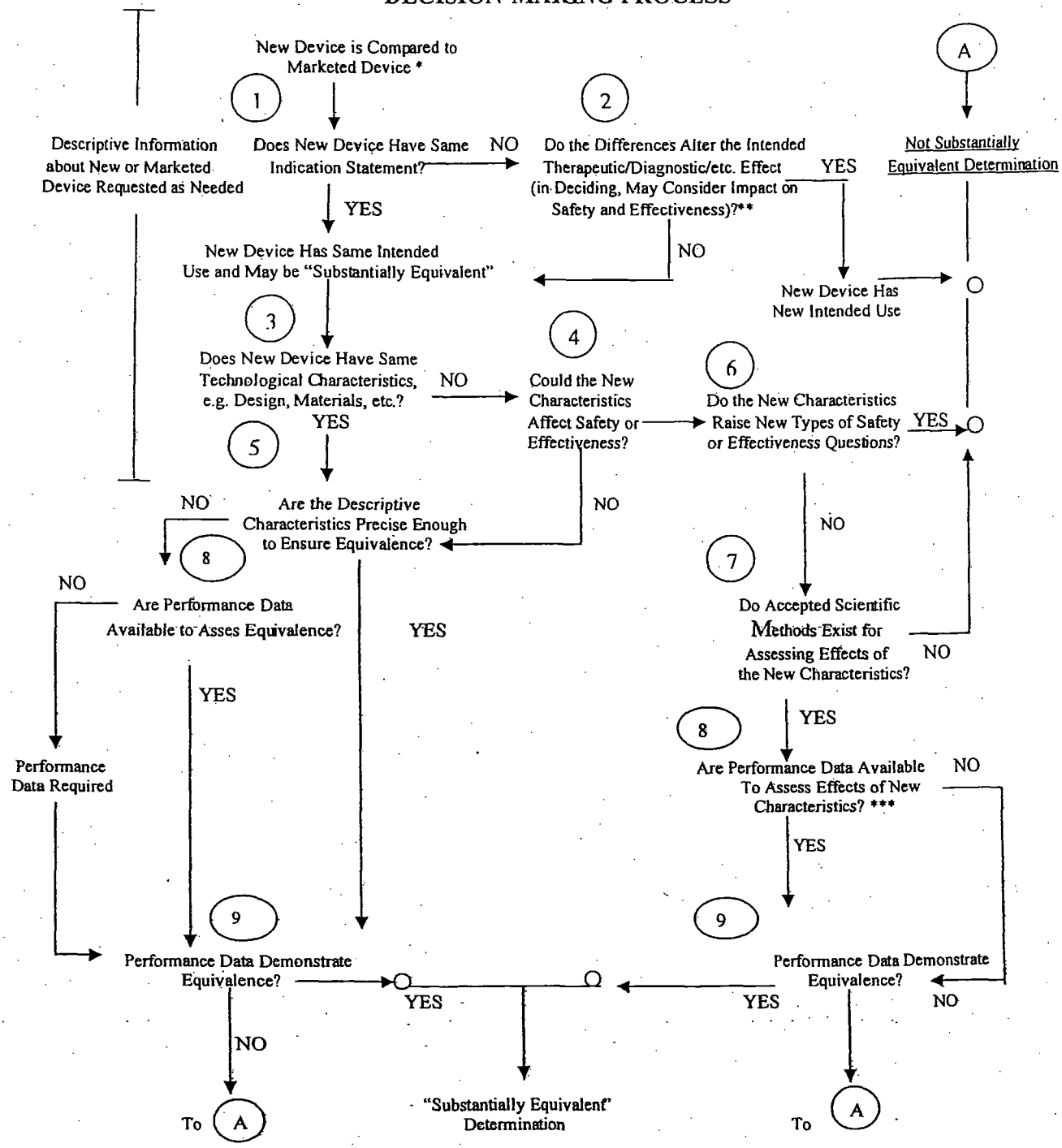
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
QUICK REVIEW DECISION MEMO

Reviewer: Paula Caposino

510(k) #: k121214
510(k) Holder: Beckman Coulter
Device Name: Access AccuTnI Reagent and Calibrator for use on the Access 2 Immunoassay Systems

Regulation Number: 21 CFR § 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: Class II
Product Code: MMI

ASSESSMENT SUMMARY

The initial assessment should be completed within one week of being assigned a new Traditional 510(k) submission. Send completed forms to Frances Daniel (Frances.Daniel@fda.hhs.gov), who is collecting data to evaluate the pilot Triage program.

Quick Review Criteria	Yes	No
1. The division has review experience and knowledge of expected device performance	X	
2. An extensive consult is not required		X
3. TPLC checklist does not raise new postmarket issues		
4. Quick Review checklist only raises minor issues		
5. Division Concurrence		
Comments (optional):		

***Note**: If an answer to **1 or 2** is "No", you do not need to complete the rest of the table or checklists. You can delete sections of the document that were not completed and use the traditional review template. Add the completed portion of this document to the record file of this submission.*

*If the answers to **1...4** are all "Yes", first obtain management concurrence for a "quick" review and then email the sponsor (see the TriageProgramSummary.doc for email templates). Note a 510(k) Summary is also required for Quick Review, but it can be obtained and/or revised interactively.*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Medical Officer Consultation

510(k) number: k121214
Sponsor: Beckman-Coulter
Name of device:

Scientific Reviewer:
Paula Caposino, PhD
FDA/CDRH/OIVD

Medical Officer:
Jacqueline Wieneke, MD
FDA/CDRH/OIVD

Date: June 15, 2012

Reason for Consultation:

Clinical questions:

- Does the clinical study population support the intended use
- Is the device safe to use for the intended use

Intended use: The Access AccuTnI assay is a paramagnetic particle chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patient with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction or increase probability of ischemic events requiring urgent revascularization procedures.

Clinical Comments:

1. Intended use:

- Sponsor did not submit new data to support a risk stratification claim. Therefore FDA will review only the diagnostic claim.
- Very broad claim: no intended use population indicated

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- Upon review of IUs of other cleared devices, this is consistent

2. Clinical studies:
   - Reference Interval Trial to determine 99th percentile of normal, Upper Reference Limit (URL): acceptable study design
     - The analysis determined the 99th percentile URL to be 0.02 ng/mL (95% CI: 0.01-0.05 ng/mL)
   - Feasibility Study to determine cut-off values for diagnosis of MI to be validated in the pivotal trial: acceptable study design
     - The analysis determined that a cutoff of 0.03 mg/ml would yield 95% sensitivity; therefore an estimated cutoff of 0.03 ng/mL (95% CI: 0.02-0.04 ng/mL) is proposed for validation in the pivotal trial
   - Pivotal Trial for clinical performance:
     - Study population relative to intended use population (p 9-36 and 9-39)
       - The study evaluates "all comers" presenting to Emergency Depts (ED) with chest pain or equivalent ischemic symptoms suggestive of ACS
         - I assume the test will be used in other patient settings such as patients presenting to physician offices with ACS symptoms and patients in hospital for other reasons, i.e. post-op patients, who develop ACS symptoms. These types of patient settings are not evaluated in this clinical study.
         - There is no specific intended use population indicated in the IU statement
           - As indicated earlier, this is consistent with other cleared devices
     - Inclusion criteria (p 9-39)
       - Presentation to ED chest pain occurring "at rest"
         - What is the definition of "at rest"?
         - What about patients presenting with chest pain following exercise or other stressful situations?
         - Were any patients excluded based on this criterion?
     - Number of subjects by site and diagnosis (p 9-45)
       - I notice that 2 of the original sites (03, 05) have been left out
       - What is the reason for eliminating these sites from the analysis?

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- Performance estimates: Sensitivity, Specificity NPV and PPV (note*: my comments on performance criteria are based on the reported statistical analysis taken at face value. I have not seen the actual data and have not seen the biostatician's comments on the validity of the analysis.)*

  - I do note that a significant portion of the original 253 adjudicated MI patients are lost by the 6-9 hour time period. The study protocol calls for:

    A minimum of 3 blood draws within 24 hours of presentation is desirable (collected at presentation and at every standard-of-care follow-up draw). However, 2 blood draws are acceptable when immediate intervention is required per standard-of-care, and a 3rd draw could not be obtained without delaying treatment. (Restricting the study to only those subjects with ≥3 samples would lead to selection bias by eliminating the majority of MI patients who receive timely reperfusion therapy per the American Heart Association's "Get With The Guidelines" recommendations.)

    - I recognize that some patients did not get subsequent draws due to diagnosis and treatment or discharge; however, there seems to be a significant deviation from the protocol as it appears that the majority of the patients did not get the "minimum of 3 blood draws" as per the study design. I believe it would be prudent to examine the data to determine how these patients were evaluated and treatment/discharge decisions were determined.
    - With that said, I will comment on the available statistical data as reported by the sponsor.
  - Performance estimates are reported using time intervals
    - *after presentation to ED*: baseline, 1-3 hours, 3-6 hours, 6-9 hours
    - *after symptom onset*: < 8 hours and ≥ 8 hours after symptom onset
      - Some clinicians may also want to see performance characteristics at < 12 hours and ≥ 12 hours after symptom onset
      - The American College of Emergency physicians (ACEP) recommends serial troponin measurements if patient presents < 8 hours after symptom onset; a single

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negative troponin measured ≥ 8 hours (8-12 hours) after symptom onset may be used to rule out MI in the Emergency Dept in the context of the patient's clinical presentation and history. (Fesmire FM. Ann Emerg Med 2006;48:270-301).

- Keep in mind, patients' estimates of symptom timing may not be totally reliable.

- Cut offs: 0.02 ng/mL vs. 0.03 ng/mL
  - 0.02 ng/mL is the 99th percentile cut off; as per the "points to consider", a suitable cut off should be based on the 99th percentile of normal (URL)
  - The sponsor's analysis determined that a cutoff of 0.03 mg/ml would yield 95% sensitivity; therefore an estimated cutoff of 0.03 ng/mL (95% CI: 0.02-0.04 ng/mL) is proposed for validation in the pivotal trial
  - What is the CV at each of these cut-offs: does the device achieve the required maximum 10% CV allowable at each of these cut-offs?
  - Why has the firm chosen the 0.03 ng/ml cut-off rather than the 99th percentile cut-off, 0.02 ng/mL (which yields 98% sensitivity), as suggested in the point to consider?
- Sponsor should clarify: Were the performance estimates determined using both the serum and lithium heparin samples? I only see one set of data and no indication if the results are from the serum or plasma samples. They did perform matrix comparison study but do we require clinical validation of both matrices for troponin?

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- **Sensitivity, Specificity NPV and PPV:** ***time after presentation to ED***

Baseline						
	Sensitivity			Specificity		
Tnl cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	92.1	233/253	88.8 - 95.4	84.3	1412/1675	82.6 - 86.0
0.03	87.4	221/253	83.3 - 91.4	89.3	1495/1675	87.8 - 90.7
0.04	77.1	195/253	71.9 - 82.3	93.9	1572/1675	92.7 - 95.0
0.05	65.6	166/253	59.8 - 71.5	95.6	1602/1675	94.7 - 96.6
0.06	59.7	151/253	53.6 - 65.7	97.0	1625/1675	96.2 - 97.8
0.10	44.7	113/253	38.5 - 50.9	98.6	1651/1675	98.0 - 99.1
0.20	30.8	78/253	25.1 - 36.5	99.4	1665/1675	99.0 - 99.8
0.30	24.1	61/253	18.8 - 29.4	99.6	1669/1675	99.4 - 99.9
0.40	20.2	51/253	15.2 - 25.1	99.6	1669/1675	99.4 - 99.9
0.50	17.8	45/253	13.1 - 22.5	99.6	1669/1675	99.4 - 99.9

1-3 Hours						
	Sensitivity			Specificity		
Tnl cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	98.4	122/124	96.2 - 100.0	85.5	867/1014	83.3 - 87.7
0.03	96.0	119/124	92.5 - 99.4	89.4	907/1014	87.6 - 91.3
0.04	89.5	111/124	84.1 - 94.9	93.5	948/1014	92.0 - 95.0
0.05	80.6	100/124	73.7 - 87.6	95.8	971/1014	94.5 - 97.0
0.06	74.2	92/124	66.5 - 81.9	97.0	984/1014	96.0 - 98.1
0.10	54.0	67/124	45.3 - 62.8	98.8	1002/1014	98.2 - 99.5
0.20	42.7	53/124	34.0 - 51.4	99.4	1008/1014	98.9 - 99.9
0.30	33.1	41/124	24.8 - 41.3	99.5	1009/1014	99.1 - 99.9
0.40	28.2	35/124	20.3 - 36.1	99.6	1010/1014	99.2 - 100.0
0.50	25.0	31/124	17.4 - 32.6	99.7	1011/1014	99.4 - 100.0

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3-6 Hours						
	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	98.1	154/157	95.9 - 100.0	81.0	762/941	78.5 - 83.5
0.03	94.9	149/157	91.5 - 98.3	86.7	816/941	84.5 - 88.9
0.04	87.3	137/157	82.0 - 92.5	93.0	875/941	91.4 - 94.6
0.05	79.0	124/157	72.6 - 85.4	95.0	894/941	93.6 - 96.4
0.06	72.0	113/157	64.9 - 79.0	96.4	907/941	95.2 - 97.6
0.10	54.8	86/157	47.0 - 62.6	98.3	925/941	97.5 - 99.1
0.20	41.4	65/157	33.7 - 49.1	99.3	934/941	98.7 - 99.8
0.30	32.5	51/157	25.2 - 39.8	99.6	937/941	99.2 - 100.0
0.40	29.3	46/157	22.2 - 36.4	99.6	937/941	99.2 - 100.0
0.50	27.4	43/157	20.4 - 34.4	99.6	937/941	99.2 - 100.0

6-9 Hours						
	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	93.0	40/43	85.4 - 100.0	76.4	188/246	71.1 - 81.7
0.03	90.7	39/43	82.0 - 99.4	87.0	214/246	82.8 - 91.2
0.04	90.7	39/43	82.0 - 99.4	93.1	229/246	89.9 - 96.3
0.05	86.0	37/43	75.7 - 96.4	94.7	233/246	91.9 - 97.5
0.06	79.1	34/43	66.9 - 91.2	95.9	236/246	93.5 - 98.4
0.10	74.4	32/43	61.4 - 87.5	98.4	242/246	96.8 - 100.0
0.20	53.5	23/43	38.6 - 68.4	98.8	243/246	97.4 - 100.0
0.30	44.2	19/43	29.3 - 59.0	98.8	243/246	97.4 - 100.0
0.40	41.9	18/43	27.1 - 56.6	99.2	244/246	98.1 - 100.0
0.50	34.9	15/43	20.6 - 49.1	99.2	244/246	98.1 - 100.0

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- **Table below shows previous cleared devices with corresponding Se and Sp (K110851 which was NSE'd)**

Submission Number	Test Name	Cut-off (ng/mL)	Time (hours)	Sensitivity	Specificity
K110851	**Alere Cardio3**	**0.022**	**0 6**	**73% 83%**	**96% 95%**
K080269 (k030286)	Alere CardioProfilER	0.4	0-6 6-12 12-24	65% 72% 93%	100% 97% 95%
K082699	Elecsys Roche TnI	0.3	0-6 6-12 >12	81% 85% 91%	98% 99% 96%
k063243	bioMerieux VIDAS	0.11	0-6 4-12	70% 97%	96% 96%
k062838	Ortho Vitros	0.12	0-6 6-12 12-24	70% 89% 90%	96% 94% 94%
K060875 (k041811)	Abbott AxSYM	0.4	0-6 6-12 12-24	60% 78.6% 91.7%	97.4% 96.1% 98.3%
k100130	**Mitsubishi PathFast**	**0.03**	**0-2 2-6 6-12**	**73.6% 93.1% 91.7%**	**92.7% 93.1% 91.6%**

- **For *time after presentation to ED* sensitivity is comparable (and in some cases better, i.e. at baseline) to the previously cleared devices; however specificity is significantly sacrificed**

Cutoff	Hours After Admission	Sensitivity	Specificity
0.02 ng/mL	Baseline	92%	84%
	1-3 Hours	98%	86%
	3-6 Hours	98%	81%
	6-9 Hours	93%	76%
0.03 ng/mL	Baseline	87%	89%
	1-3 Hours	96%	89%
	3-6 Hours	95%	87%
	6-9 Hours	91%	87%

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- NPV is good (allowing reasonable rule out in ER) but PPV is significantly lower leading to more people being held in ED unnecessarily (a significant percentage of people with positive results actually do not have disease)

Results for ROC Cutoff (0.03 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Admission	PPV (95% CI)	n/N	NPV (95% CI)	n/N
Baseline	55.1 (50.2 - 60.0)	221/401	97.9 (97.2 - 98.6)	1495/1527
1-3 hours	52.7 (46.1 - 59.2)	119/226	99.5 (99.0 - 99.9)	907/912
3-6 hours	54.4 (48.5 - 60.3)	149/274	99.0 (98.4 - 99.7)	816/824
6-9 hours	54.9 (43.4 - 66.5)	39/71	98.2 (96.4 - 99.9)	214/218

Results for URL (0.02 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Admission	PPV (95% CI)	n/N	NPV (95% CI)	n/N
Baseline	47.0 (42.6 - 51.4)	233/496	98.6 (98.0 - 99.2)	1412/1432
1-3 hours	45.4 (39.4 - 51.3)	122/269	99.8 (99.5 - 100.0)	867/869
3-6 hours	46.2 (40.9 - 51.6)	154/333	99.6 (99.2 - 100.0)	762/765
6-9 hours	40.8 (31.1 - 50.5)	40/98	98.4 (96.7 - 100.0)	188/191

- Need to discuss this trade-off with Review team
  - High NPV limits the risk of inappropriately discharging a patient, i.e. with a high NPV the clinician can be reasonably certain that a patient with a negative test is not having MI; thus, the clinician is confident in ruling out diagnosis of MI
  - On the other hand, the lower PPV means that there is a significant number of patients who will unnecessarily be kept in hospital due to a positive test when they actually do not have MI
  - From a risk-benefit standpoint, with the use of troponin as an aid in the diagnosis in MI, a high NPV is of more importance than a high PPV (i.e. the clinical consequences of a false negative result are more severe than the consequences of a false positive result);

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this device appears to achieve appropriate NPV at both cut points: 0.02 ng/mL and 0.03 ng/mL

- Sensitivity, Specificity NPV and PPV: *time after symptom onset*
  - Keep in mind that this time interval is more difficult to determine with certainty since patients' estimates of symptom onset are not always reliable
  - None-the-less, based on the reported statistical analysis, similar comments (as those made in regard to "time after presentation to ED") on sensitivity, specificity NPV and PPV can be made

Cutoff	Hours After Symptom Onset	Sensitivity (95% CI)	Specificity (95% CI)
0.02 ng/mL	< 8 Hours	96% (94-99)	83% (81-86)
	≥ 8 Hours	97% (94-99)	82% (79-84)
0.03 ng/mL	< 8 Hours	92% (87-96)	89% (87-91)
	≥ 8 Hours	94% (91-98)	87% (85-89)

  - Sensitivity is acceptable with loss of specify
  - I do not see NPV and PPV reported for this time interval

- Method comparison study: not necessary as per points to consider
  - I have no specific comments
- Matrix comparison: defer comments (analytical performance)

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Date: June 15, 2012

From: Chava Zibman, PhD (Mathematical Statistician)

DBS/OSB/CDRH

Subject: Statistical Review for K121214, Access TnI on the Access 2 Immunoassay System, by Beckman Coulter

To: Paula Caposino

DCTD/OIVD/CDRH

Background

This is a statistical review of K121214 regarding the Access TnI assay (for Troponin) by Beckman Coulter. Pre-IDE I100255 was first submitted for the pivotal study of this assay in March 2010. No IDE was submitted. A major concern regarding this device is that its performance changes according to the temperature of the room in which the assay in analyzed. This review is concerned with the pivotal study, the sample matrix comparison, and the thermal sensitivity (impact on low dose) concordance study.

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Indications for use

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

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Pivotal Study

Study Objectives

- To evaluate the AccuTnI assay as an aid in the diagnosis of myocardial infarction (MI) in patients presenting to the Emergency Department (ED) with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS) (intended use population, "all comers").
- To assess the 99th percentile Upper Reference Limit (URL)
- To validate the pre-specified cutoff from the Feasibility Trial
- To calculate diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) over time from serial blood draws. Positive and negative predictive values will also be reported.

Note: *The protocol for this study does not appear to offer any pre-specified primary endpoints, study hypotheses, or success criteria.*

It is important to pre-specify endpoints and a statistical hypothesis before a study is conducted. If the investigators in a study, do not pre-specify the hypothesis before the study, there is the risk that any endpoints analyzed in the final analysis were chosen from a large pool of possible endpoints. This leads to the possibility that the investigator chose the most desirable results out of several possibilities and that the strength of those results occurred by chance.

The efficacy analysis was performed using plasma samples. A matrix comparison study was performed to compare plasma and serum measurements.

Study Design

Fourteen sites were included. The sponsor sought a geographically diverse group of primary care hospital-associated emergency departments (EDs) to participate in the study.

The study evaluated all adult patients presenting to the ED with chest pain or equivalent ischemic symptoms suggestive of ACS. 1,929 consecutive subjects were enrolled over the course of a year. Specimen testing was then performed at four external laboratories.

The clinical endpoint was diagnosis of MI (based on the Universal Definition of Myocardial Infarction). The troponin assay used for diagnosis of patients at each site was a FDA-cleared TnI assay which was the standard of care at each institution.

Investigators blinded to the AccTnI assay results adjudicated each subject's diagnosis to determine who had actually experience an MI.

The sponsor justified pooling across sites by asserting that all sites followed identical protocols, and all samples were tested using the same protocol. The sponsor found that efficacy was consistent across sites.

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AccuTnI results were determined on the Access 2 Instrument in singlet using 3 lots of reagent.

Statistical Analysis

- To evaluate the clinical performance of the AccuTnI assay, Sensitivity (% MI correctly diagnosed) and Specificity (% Non-MI correctly diagnosed) were determined for serial time intervals (up to nine hours)after symptom onset and after admission to the hospital. 95% Confidence Intervals were computed. The following potential cutoffs were evaluated:
    - The 99th percentile Upper Reference Limit (URL): 0.02 ng/mL
    - The cutoff derived from ROC curve analysis of the Feasibility Trial results: 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) (Sensitivity 95.5% [84.5 - 99.4])
    - Mild to moderate elevations of troponin: Cutoffs from 0.02 to 0.50 ng/mL
- Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were also generated for serial time intervals. 95% Confidence Intervals were computed.
- Positive predictive value (PPV) and negative predictive value (NPV) are also reported.
- Statistical analyses were performed using SAS System software (version 9.2), with a p value less than 0.05 indicating statistical significance. All statistical comparisons were two-tailed, and performed using Fisher's Exact test for dichotomous variables, and t-test, ANOVA, or Wilcoxon test for continuous variables depending upon data distribution and normality.

Note: *This review is concerned only with results based on the 0.03 ng/mL cutoff.*

Results of Pivotal Study

The study included 1929 subjects on whom 4625 blood draws were taken. 253 subjects were determined by the adjudication committee to have had an MI.

Data were first analyzed according to whether a draw occurred <8 hours or ≥8 hours after the onset of symptoms.

There were 1158 unique subjects who had observations taken within 8 hours of the onset of symptoms. 165 of these had MI. Within these observations, the AUC was 0.96 with a 95% CI of [0.95-0.97]. At the 0.03 ng/mL cutoff, sensitivity was estimated at 91.5% with a CI of [87.3, 95.8]. Specificity was estimated at 89.1% with a CI of [87.2, 91.1].

There were 1272 unique subjects who had observations taken at least 8 hours following the onset of symptoms. 159 of these had MI. Within these observations, the AUC was 0.96 with a 95% CI of [0.94-0.98]. At the 0.03 ng/mL cutoff, sensitivity was estimated at 94.3% with a CI of [90.7, 97.9]. Specificity was estimated at 86.8% with a CI of [84.8, 88.8].

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Positive predictive value (PPV) and negative predictive value NPV) are provided in the table below:

Results for ROC Cutoff (0.03 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Symptom Onset	PPV (95% CI)	n/N	NPV (95% CI)	n/N
< 8 hours	58.3 (52.3 - 64.3)	151/259	98.4 (97.6 - 99.3)	885/899
≥ 8 hours	50.5 (44.8 - 56.2)	150/297	99.1 (98.5 - 99.7)	966/975

Note: *The sponsor correctly comments that PPV and NPV are dependent on prevalence of MI. Populations with different rates of MI will demonstrate different PPV and NPV values.*

Question for sponsor: *According to the sponsor, when a subject has more than one observation <8 or ≥8 hours following the onset of symptoms, only one observation is used in the analysis. How is it determined which observation is included? Ideally, all available observations should be included in the analysis with adjustments made to account for the correlation between repeat measurements made on individual subjects. See Emir et al's 1998 paper in* Statistics in Medicine *"Analysis of repeated markers used to predict progression of cancer".*

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The sponsor claims that no difference in efficacy AUCs were seen between sites and offers that a p value ≥0.19 was obtained.

Question for sponsor: *On page 60, you examine whether AUC varies by site. Please explain what observations were included in this analysis. That is, was it all samples? One sample per subject? You offer that you obtained a p-value of at least 0.19 but do not explain what hypothesis was tested. Please provide this hypothesis. Without knowing what hypothesis was tested on what data, FDA cannot assess the validity of your finding.*

To further justify pooling by site for the efficacy analysis, please provide FDA with a calculation of the proportion of subjects with MI by site, with 95% confidence intervals. Please also provide estimates of sensitivity and specificity, by time from onset of symptoms, with 95% confidence intervals. Please perform the same analysis by time from hospital admission.

Data were also analyzed according to whether blood draws occurred at baseline, 1-3 hours, 3-6 hours, or 6-9 hours following hospital admission.

Questions for sponsor: *When a subject has more than one observation in a given interval, were all observations included or only one? As far as I can tell, there were at least 60 cases in which a subject had more than one draw in a given interval. If all were included, the sponsor should adjust the analysis to account for correlation between those*

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observations. If only one was included, the sponsor should explain how that observation was selected.

According to the line data, all 1929 subjects have draws at time zero. There are 21 additional draws occurring between 0.1 and 0.9 hours after baseline. Are these 21 draws not included in the analyses? Are the 70 draws that occurred exactly 3 hours after baseline considered to be in the 1-3 or 3-6 bin? Similarly are the 38 draws that occurred at exactly 6 hours in the 3-6 hour bin or the 6-9 hour bin? There are another 70 draws taken more than 9 hours after baseline. Are these excluded from analyses?

Not all subjects had blood draws taken in all intervals. As per standard of care, subjects who were diagnosed (correctly or not) as having or not having an MI did not have further measurements taken. Some subjects had intervals without observations followed by intervals in which observations were obtained. For instance 82 subjects only had observations at baseline and at 6-9 hours. By my estimate, over 30% of the subjects had intervals with no values in between intervals with missing values.

Question for sponsor: *There is substantial variation in the number of subjects tested at each time interval. Please explain how the population of subjects evaluated at each time interval is representative of the intended use population at that time interval. Please also examine how many subjects are missing a value in between observations (for example, have observations at baseline and 6-9 hours only) and explain why these missing values occurred.*

Efficacy results, by time since hospital admission are illustrated in the tables below.

Area Under the Curve, by time since admission

Hours after admission	AUC (95% CI)
Baseline	0.94 (0.92, 0.95)
1-3 hours	0.97 (0.96, 0.98)
3-6 hours	0.96 (0.95, 0.98)
6-9 hours	0.94 (0.89, 0.99)

Sensitivity and Specificity with the 0.3 ng/mL cutoff, by time since admission

	Sensitivity			Specificity		
Hours after admission	%	n/N	95% CI	%	n/N	95% CI
Baseline	87.4	221/253	83.3-91.4	89.3	1495/1675	87.8-90.7
1-3 hours	96.0	119/124	92.5-99.4	89.4	907/1014	87.6-91.3
3-6 hours	94.9	149/197	91.5-98.3	86.7	816/941	84.5-88.9
6-9 hours	90.7	39/43	82.0-99.4	87.0	214/246	82.8-91.2

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Note: *Particularly for smaller samples and for estimates of proportions close to 1, the Wald confidence intervals offer less accurate more favorable results than exact confidence intervals. For example, the 95% CI for sensitivity at 6-9 hours is [77.9-97.4] using the exact method. This is noticeably lower than the [82.0-99.4] calculated by the sponsor using Wald. The sponsor should repeat their analysis using exact confidence intervals for all confidence intervals regarding proportions.*

Results for ROC Cutoff (0.03 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Admission	PPV (95% CI)	n/N	NPV (95% CI)	n/N
Baseline	55.1 (50.2 - 60.0)	221/401	97.9 (97.2 - 98.6)	1495/1527
1-3 hours	52.7 (46.1 - 59.2)	119/226	99.5 (99.0 - 99.9)	907/912
3-6 hours	54.4 (48.5 - 60.3)	149/274	99.0 (98.4 - 99.7)	816/824
6-9 hours	54.9 (43.4 - 66.5)	39/71	98.2 (96.4 - 99.9)	214/218

Sample Matrix Comparison

I reviewed section 8.10 of the submission and its associated data. In this study, samples were taken from 103 subjects. Samples were measured in replicate using both serum and lithium heparin plasma at temperatures of 18, 23, and 28 degrees Celsius. Thus there were 103*2*2*3=1236 measurements taken. Troponin values in this range spanned from 0.006 to 77.961

The sponsor took the averages for each pair of replicates and performed a Passing-Bablok regression comparing the matrices at each temperature. Passing-Bablok is a form of regression that, unlike ordinary least squares regression, accounts for the presence of measurement error in measurements made by each matrix.

Deleted: The analysis here assumes an equal amount of measurement error within each matrix.

The sponsor obtained the following results for the intercepts. I was able to replicate this analysis.

Table 62: Lithium Heparin Plasma vs. Serum Comparison

Temperature	Dose Range (ng/mL)		Slope	95% CI		r-value	n
	Low	High		Lower	Upper		
18°C	0.006	77.961	**1.03**	1.02	1.06	**0.99**	103
23°C	0.007	71.841	**1.02**	0.99	1.04	**0.99**	103
28°C	0.006	66.761	**1.04**	1.01	1.06	**0.99**	103

The sponsor did not offer intercepts, but I obtained an intercept of 0.00 (95% CI [-0.01, 0.00]) for the comparison at all three temperatures.

Using only the first of the two replicates for each measurement, I obtain:

Temperature	Dose Range	Slope	95% CI	N	Inter	95% CI

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	(ng/mL)						-cept		
	Low	High		Lower	Upper			Lower	Upper
18°	0.006	79.956	1.04	1.02	1.06	103	0.00	-0.01	0.00
23°	0.007	71.906	1.01	0.99	1.05	103	0.00	-0.01	0.00
28°	0.007	65.543	1.04	1.01	1.06	103	0.00	-0.01	0.00

Using only the second of the two replicates for each measurement, I obtain:

Temperature	Dose Range (ng/mL)		Slope	95% CI		N	Inter -cept	95% CI	
	Low	High		Lower	Upper			Lower	Upper
18°	0.006	75.966	1.03	1.01	1.06	103	0.00	-0.01	0.00
23°	0.007	71.776	1.02	1.00	1.05	103	0.00	0.00	0.00
28°	0.005	67.979	1.04	1.02	1.05	103	0.00	-0.01	0.00

Figures depicting the relationships between measurements taken using each matrix at each temperature are below in the sponsor's figures 8, 9, and 10.

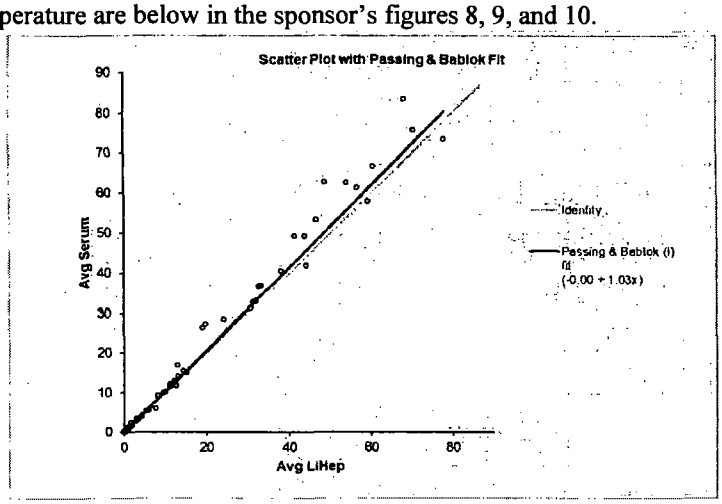

Figure 8: Passing-Bablok Plot, 18°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL

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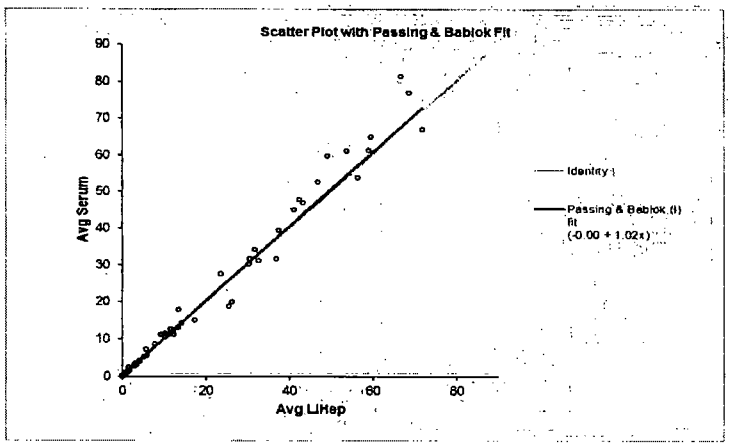

Figure 9: Passing-Bablok Plot, 23°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL

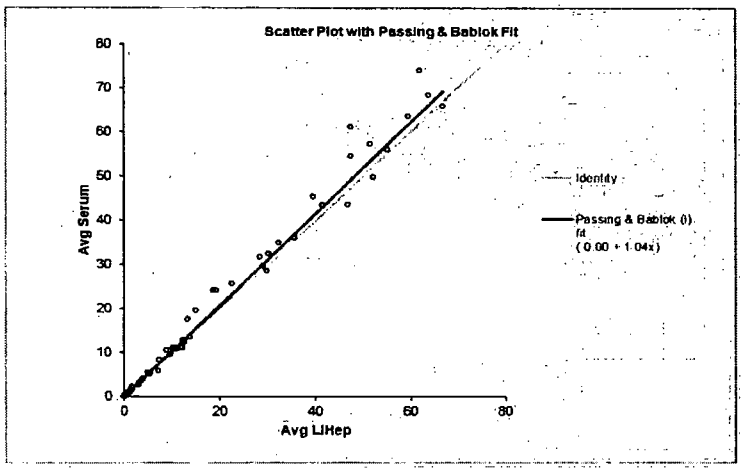

Figure 10: Passing-Bablok Plot, 28°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL

Question for sponsor: *Please explain how the samples used in the matrix comparison study were chosen out of the general study population.*

Note to OIVD: *It may be worthwhile to observe the matrix comparison in specific ranges, particularly near the cutoff value. If OIVD is concerned with the difference between results obtained using ordinary least squares regression versus Passing-Bablok, we should ask the sponsor to explain what features of the data led them to choose Passing-Bablok as*

Deleted: *My exploratory analysis suggests that the regression results do not change noticeably when higher troponin levels are removed from analysis, but it*

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opposed to, for example, Deming regression. We should also ask them how (as seen in each matrix comparison study) imprecision differs between the two matrices.

Thermal Sensitivity—Impact on Low Dose Concordance/Agreement

This study is presented in section 8.13 of the submission. I also reviewed the line data.

In this study, 220 lithium plasma samples near the cutoff were tested using two reagent pack lots (one per subject). Half the samples were tested in duplicate at room temperatures of 18, 22, and 26 degrees Celsius. The remaining samples were tested, also in duplicate, at 20, 24, and 28 degrees. There would therefore be 660 observations if there were no missing values, but 28 values at 22 degrees are missing. Analysis was performed after averaging the duplicate measurements together.

According to the sponsor:

> A McNemar analysis was performed to determine whether the number of mismatched comparisons was due to random scatter or a systematic difference. For this analysis, a p-value ≥0.05 represents random variability (non-significant). If p was <0.05 (significant), concordance was evaluated. In addition, bias between low and high temperature was computed using a log-log regression fit.
>
> Acceptance Criteria: Per the AccuTnI Design Inputs, the McNemar p-value must be non-significant (≥0.05). If the p-value is significant, concordance must be ≥90%. Bias at the cutoffs must be ≤0.0084 (SD specification).

Comments to sponsor: *A p-value above 0.05 does not prove that there is no meaningful bias. A more appropriate acceptance criteria would require that the study prove that the level of disagreement between measures taken at different temperatures be statistically significantly below a pre-specified clinically acceptable level. Confidence intervals (accounting for repeated measures on individual subjects) should be provided for all measures of agreement.*

The sponsor found that, in all comparisons of measurements taken on the same sample at different temperatures (averaging the duplicates taken for each measurement), there was agreement in 91% of the cases in terms of whether the values fell >0.03 or ≤0.03 ng/mL.

Of 604 comparisons, both values were at or below the cutoff in 274 cases. Both were above the cutoff in 275 cases. In two cases, the value was above the cutoff when measured at the lower temperature but at or below the cutoff at the high temperature. In 53 cases, the measurement was at or below the cutoff when measured at the lower temperature but above the cutoff at the high temperature.

I performed further analysis using Passing-Bablok regression. The estimates of the intercepts in these regression was always 0, but, for example, the slope in the comparison between measurements taken at 20 and 28 degrees was 1.46 with a 95% confidence

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interval of (1.36, 1.54). Higher temperatures consistently yielded higher troponin measurements.

The proportion of observations above 0.03 varies by temperature as follows (recall that samples were tested at 18, 22, and 26 degrees or at 20, 24, and 28 degrees). As previously observed, in the case of nearly all discrepancies, a sample was negative at the lower temperature and positive at the higher temperature.

temp	18 Celsius	22 Celsius	26 Celsius
% above cutoff	46.4 (51/110)	47.6 (39/82)	55.5 (61/110)

temp	20 Celsius	24 Celsius	28 Celsius
% above cutoff	42.7 (47/110)	48.1 (53/110)	57.3 (63/110)

Comment [a1]: Did you try using Fisher-Freeman-Halton (generalization of Fisher's Exact Test to more than 2 categories) to test for significance? If the results are significantly different across temperatures, then this bolsters the case that temperature matters. It would help if the fractions used to obtain these percentages were presented in these tables.

I do not believe that the assay demonstrates concordance across temperatures.

If you have any questions about this review, please contact me at (301) 796-5325 or at

chava.zibman@fda.hhs.gov.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Zibman, Chava
Sent: Tuesday, June 19, 2012 4:22 PM
To: Caposino, Paula
Subject: RE: Regression of the thermal concordance data

all using Passing-Bablok

18 vs 22 slope: 1.16 (95% Confidence interval [1.11, 1.22]) intercept: 0.00 [0.00,0.00]
18 vs 26 slope 1.33[1.26, 1.40] intercept: 0.00 [-0.01, 0.00]
22 vs 26 slope 1.17 [1.12, 1.22] intercept: 0.00 [-0.01, 0.00]
20 vs 24 slope 1.24[1.20, 1.28] intercept: 0.00 [0.00, 0.00]
20 vs 28 slope 1.46 [1.37, 1.54] intercept: 0.00 [-0.01, 0.00]
24 vs 28 slope 1.17 [1.13, 1.21] intercept: 0.00 [0.00, 0.00]

From: Caposino, Paula
Sent: Tuesday, June 19, 2012 3:08 PM
To: Zibman, Chava
Subject: Regression of the thermal concordance data

Dear Chava,
Do you have the other slopes for these comparisons? It may make our case stronger to include all of the analysis?

We performed further analysis using Passing-Bablok regression. The estimates of the intercepts in these regression was always 0, but, for example, the slope in the comparison between measurements taken at 20 and 28 degrees was 1.46 with a 95% confidence interval of (1.36, 1.54). Based on this analysis and the analysis provided in the table above in 1aii, we have serious concerns that higher temperatures consistently yielded higher troponin measurements. Therefore, we do not believe that the data provided demonstrates concordance across temperatures.

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIVD, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

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Caposino, Paula

From: Zibman, Chava
Sent: Monday, June 18, 2012 4:01 PM
To: Caposino, Paula
Subject: final draft Statistical Review for K121214, Access TnI on the Access 2 Immunoassay System, by Beckman Coulter
Attachments: CZ_review_K121214 FINAL.doc

Attached is my final draft.

I still maintain that Passing-Bablok is appropriate for the matrix comparison study, and Arkendra, my acting team leader, agrees. That said, if you are concerned, you should ask the sponsor how the data meet the assumptions that Passing-Bablok regression calls for. The precisions using serum and lithium heparin look comparable in the study I looked at, but it may be worth looking at the precisions as measured in the other matrix comparison study in order to get a better sense of what form of regression is called for.

Chava

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Zibman, Chava
Sent: Monday, June 18, 2012 10:40 AM
To: Caposino, Paula
Subject: RE: matrix comparison results

yes

From: Caposino, Paula
Sent: Monday, June 18, 2012 10:39 AM
To: Zibman, Chava
Subject: RE: matrix comparison results

for singlicate too?

From: Zibman, Chava
Sent: Monday, June 18, 2012 10:39 AM
To: Caposino, Paula
Subject: RE: matrix comparison results

The intercepts are almost always estimated at zero with a 95% CI of (-0.01, 0.00). I can add them to the tables.

From: Caposino, Paula
Sent: Monday, June 18, 2012 10:38 AM
To: Zibman, Chava
Subject: RE: matrix comparison results

what about intercepts

From: Zibman, Chava
Sent: Monday, June 18, 2012 10:37 AM
To: Caposino, Paula
Subject: matrix comparison results

The results don't change much according to whether one or both replicates are used. I added these analyses to my review draft.

Averaging the two replicates:

Table 62: Lithium Heparin Plasma vs. Serum Comparison

Temperature	Dose Range (ng/mL)		Slope	95% CI		r-value	n
	Low	High		Lower	Upper		
18°C	0.006	77.961	1.03	1.02	1.06	0.99	103
23°C	0.007	71.841	1.02	0.99	1.04	0.99	103
28°C	0.006	66.761	1.04	1.01	1.06	0.99	103

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Using only the first of the two replicates for each measurement, I obtain:

Temperature	Dose Range (ng/mL)		Slope	95% CI		N
	Low	High		Lower	Upper	
18°	0.006	79.956	1.04	1.02	1.06	103
23°	0.007	71.906	1.01	0.99	1.05	103
28°	0.007	65.543	1.04	1.01	1.06	103

Using only the second of the two replicates for each measurement, I obtain:

Temperature	Dose Range (ng/mL)		Slope	95% CI		N
	Low	High		Lower	Upper	
18°	0.006	75.966	1.03	1.01	1.06	103
23°	0.007	71.776	1.02	1.00	1.05	103
28°	0.005	67.979	1.04	1.02	1.05	103

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Callaghan, Jim
Sent: Friday, June 15, 2012 10:09 AM
To: Caposino, Paula
Subject: RE: [CTS ALERT] Consult CON129426 is coming due [June 15, 2012]
Attachments: New software and hardware review issues.

Paula

I am closing this out. I looked at the open software review issues of IUO version verses IVD 3.3 release version and unresolved anomalies this is what I came up with.

Additional work items were created for issues identified during verification and validation testing. These work items were corrected, verified and closed in software release 3.3 or deferred to a future release. Work items generated during formal testing were closed with code correction, closed with no code change or deferred to a future release and listed in the unresolved anomalies list. The additional work items are described in the Access 2 3.3 Software Testing and Software Validation Summary.

They have completed testing based on the IUO build to the IVD build and completed verification of work items to close out release version of 3.3. I looked at the remaining anomalies and concur with their assessment that they do not impact safety and effectiveness. The other issues we discussed and you put together in email attached, for details on algorithms, tested instruments.... Still are at issue.

Jim

From: CDRH Center Tracking System [mailto:cdrhcts@cdrh.fda.gov]
Sent: Friday, June 15, 2012 6:16 AM
To: Callaghan, Jim
Subject: [CTS ALERT] Consult CON129426 is coming due [June 15, 2012]

June 15, 2012 This consult is coming due [June 15, 2012] in the Center Tracking System (CTS) :

Consult Number	CON129426
Consult Type	Instrumentation
Parent Document #	K121214
Requestor	Paula Velasco Caposino
Requestor Home	CDRH\OIVD\DCTD\CTXB
Consult Home	CDRH\OIVD\DCTD\CHTB

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Consultant James Callaghan

Due Date June 15, 2012

You may visit the Center Tracking System (CTS) at: http://webapps.cdrh.fda.gov/division-tracking for more information.

Please contact Paula Velasco Caposino [PVV] at paula.caposino@fda.hhs.gov or 301-796-6160 if you have any questions or comments.

This is an automated e-mail. Please do not reply to this message.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Caposino, Paula
Sent: Tuesday, June 05, 2012 7:02 PM
To: Callaghan, Jim
Subject: New software and hardware review issues.

Follow Up Flag: Follow up
Due By: Wednesday, June 06, 2012 4:00 PM
Flag Status: Red

Attachments: Document2.doc

Document2.doc (25 KB)

Please see my revised software and hardware issues based on my understanding of todays meeting for your files.

Thanks for your help with this.
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Software and Hardware Issues:

X. Algorithm: You have not provided detailed information about the algorithm. Therefore, please provide more information about your algorithm. Please describe the algorithm, how it works and please discuss how the algorithm was developed.

X. DxI Intrument: The purpose of Appendix 5 is described as "this document contains generalized requirements for thermal monitoring on both Access 2 and DxI." Appendix 10 also discuses software requirements for the DxI instrument. Meanwhile Appendix 13 page 5 states "since this implementation was done on DxI originally and fully verified before being merged to Access 2, only performing regression unit tests." On page 8 of Appendix 13 you state "run regression tests on merged code from DxI". Appendix 14, page 33 also lists "Merge calibration and result temperature calculation from DxI." On page 94 of appendix 14 you list "merged from DxI: Load new APF thermal data." On page 103 of appendix 14 you list "merge AP XML schema definition (XSD) file from DxI branch." On page 120 of appendix 14 you list "merge thermal correction database updates from DxI to Access 2 XP."
   a. All software verification and validation activities need to be fully performed on the Access 2 instrument in order to market this instrument with this software.
   b. In the current submission, we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay System.

X. Additional software: Appendix 7, 8, 9 and 10 discuss the NexStep configuration. This is described as a "configuration of Access instruments that allows the laboratory to network several Access instruments together to manage the instrument data, both results, supplies and setup information from one PC." Please be advised that in the current submission we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay Systems using Access 2 3.3 software.

X. Testing on other assays: In the description of your software testing (page 6-27 to 6-28), you state "This testing verifies the capability of the Access 2 system software version 3.3 to: apply an algorithm to adjust the dose result for thermally sensitive assays and the capability to run a "U" Command introduced in specific assay protocol files." On page 6-23 you describe testing as "verifies that the thermal algorithm implementation has not impacted other assay types. Perform test case TST1 (quantitative results)." On page 6-26, you describe testing as "verifies the input and output of quantitative, semi quantitative and qualitative assays for both thermal and non-thermal controlled assays." On pages 6-32 to 6-34 you provide a description of testing using a selected mix of assays. You state "the cumulative implementation of software features in Access 2 3.3 software did not impact the ability of the system to generate precise and accurate assay results." Appendix 22 provides results from testing using QC material on a group of assays. In the current submission, we have only reviewed the testing for the Access AccuTnI on the Access 2 Immunoassay Systems. We have not reviewed the data provided to validate the performance of any other assay. However, be advised that we do not concur with only testing QC

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samples, or only testing a select group of assays. You will need to robustly validate the performance of all assays with the new software.

Comment [p1]: Add this to file but not to Beckman.

X. IUO and IVD builds. On page 9 of Appendix 15 you state that selected Access 2 test procedures will be verified on the IVD version. The IVD version contains changes to update Help and language string files. The IVD systems software CD also has the ability to auto detect the operating system on which the software is being installed and automatically installs the correct package for the targeted operating system. We do not agree with this approach. Please verify and validate the exact IVD software version that you intend to market. If you used the IUD software version in any of the clinical studies (reference interval trial, pivotal efficacy trial and matrix comparison trial), please justify why you believe validating the IUD software version also validates the clinical performance of the IVD software.

X. Hardware: On page 7-2 you state "The case temperature sensor (thermistor) is the critical hardware component used to detect small changes in temperature, and has an accuracy specification of ± 0.2°C. This specification of ± 0.2°C was 100% verified by the supplier. Manufacturing release procedures for new instruments ensure that verified thermistors are installed." You will need to ensure that all instruments running this assay have the verified thermistors installed.

For the file but not for Beckman:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Wieneke, Jacqueline
Sent: Friday, June 15, 2012 4:13 PM
To: Caposino, Paula
Subject: RE: k121214 Beckman TnI (Medical consult - JAW)

Attachments: 510K Beckman cTnI Med consult JAW (final) June 15, 2012.doc

Hi Paula, please find attached my clinical comments. I think it will be helpful when we have a chance to see the statistical comments and if necessary, I can revise or add to it.
If you have any questions or need me to clarify anything please just let me know. This is the first troponin 510K I have worked on so I may not pick up on all of the issues.

Thanks! Jackie

510K Beckman cTnI Med consult ...

Jacqueline Wieneke, MD
Medical Officer, Pathologist, Office of In-Vitro Diagnostics
ph:301-796-6174
jacqueline.wieneke@fda.hhs.gov

FDA, White Oak Campus
10903 New Hampshire Ave.
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Silver Spring, MD 20993

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Wednesday, June 06, 2012 9:44 AM
To: Caposino, Paula
Cc: Chuck Willand; Scott T Cundy; Valynda Machen; Kurtis R Bray
Subject: RE: K121214 request for clinical data analysis clarification

Hello Dr. Caposino

The samples for the Matrix Comparison study are included on the clinical trial data diskette. Those samples used for the study have both serum and plasma results. 107 samples were included in the Matrix Comparison study.

Please let me know if you need additional information to identify these samples.

Thanks
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

06/05/2012 05:13 PM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc Chuck Willand <CWilland@beckman.com>, Scott T Cundy <STCundy@beckman.com>, Valynda Machen <vmachen@beckman.com>
Subject RE: K121214 request for clinical data analysis clarification

Hi Cindy,
Did you ever get me the raw data for the Matrix Comparison Study presented as part of the clinical trial (p. 9-96)?
Thanks,
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Monday, June 04, 2012 2:55 PM
To: Caposino, Paula
Cc: Chuck Willand; Scott T Cundy; Valynda Machen
Subject: RE: K121214 request for clinical data analysis clarification
Attachments: K121214 Response to Clinical Data Analysis Questions - June 4 2012.pdf

Hello Dr. Caposino,

Attached is the response from BEC regarding the clinical data analysis information you requested.

Please let me know if you have any questions.

Regards,

Cindy

The server made the following annotations

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Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIVD, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

RE: K121214 request for clinical data analysis clarification

Dear Dr. Caposino,

As requested, Beckman Coulter is providing the responses to your questions below:

1. Adjudicator Panel Diagnosis: The adjudication panel diagnosed 253 MIs while the site diagnosed 171 MIs (20 of which were adjudicated as non MI). Please provide the following:

a. Did the adjudication panel review the same clinical information that the site panel reviewed?

Beckman Coulter's Response:
Yes, the adjudication panel reviewed the same clinical information that the site panel reviewed. As shown in section 9.10.4.1 of the submission, the overall observed agreement between adjudicators and sites is very high (94% (151 + 1656 / 1929)).

	Site Diagnosis		
Adjudicator Panel Diagnosis	**MI**	**Non-MI**	
MI	151 (8%)	102 (5%)	253 (13%)
Non-MI	20 (1%)	1656 (86%)	1676 (87%)
	171 (9%)	1758 (91%)	1929

This phenomenon – differences between site and adjudicated diagnoses – has previously been reported in the literature (more MI's are diagnosed by adjudication panels than by sites). In fact, the adjudicators informed us during the training visits that they typically see ~75% agreement between adjudicators and sites for pharmaceutical trials in which they have previously served as adjudicators. Some level of discrepant diagnoses was expected as the objective of a centralized adjudication panel is to ensure consistency across sites and reduce

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the chance of bias as much as possible, whereas sites take physicians as they are without standardization through training. Because of the benefits of standardized central adjudication, and consistent with FDA recommendations, we used the adjudicated results in our primary endpoint analyses.

Did they have any additional/differing information?

Beckman Coulter's Response:
No, there was no difference in the information they received. The Universal Definition of MI (Thygesen et al. Circulation 2007; 116:2634-2653) was supplied to both sites and adjudicators, but clinicians also use their own judgment in determining an MI diagnosis since the universal definition does not cover all scenarios and all patient medical histories. The adjudicators told us that they tend to be more conservative when in doubt (diagnosing MI more often) since the patient was not directly visible to them.

b. Can you identify the sites at which the discordant diagnoses were found?

Beckman Coulter's Response:
Discordant diagnoses were observed at all sites.

c. How many draws did these 102 patients provide?

Beckman Coulter's Response:
The 102 patients diagnosed as Non-MI by the sites and MI by the adjudicators had an average of 2.5 draws each (256 total draws). The American College of Emergency Physicians (ACEP) guideline recommends that a single negative troponin measured ≥8 hours after symptom onset may be used to rule out MI. Despite this standard practice, all efforts were made in this study to obtain multiple serial draws per patient prior to discharge. Inclusion of this group of patients (Non-MI with few draws) in the study is of vital importance in order to prevent subject selection bias since this group represents a majority of the intended use population in clinical practice (~90% of patients presenting with chest pain are non-MI, and the objective of the ED physician is to rapidly triage and rule out MI in order to discharge these patients and focus on higher-risk patients).

2. Sensitivity and Specificity tables: While we understand that some patients diagnosed with MI may not have provided additional blood draws once they were diagnosed, we do not understand your sensitivity and specificity tables. Specifically, please provide the following information for the tables at the different blood draw time points (a-d) and for the tables at the different times since the onset of symptoms (e and f):

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a. At baseline there are 1928 subjects listed (1675 + 253) instead of 1929. Please correct or clarify.

Beckman Coulter's Response:
One patient had insufficient volume to test for the baseline sample and therefore was not included in the dataset.

b. At 1-3 hours, there are 124 MI patients and 1014 non MI patients. Please explain what happened to the missing 132 MI patients (253-124) and the missing 662 (1676-1014) non MI patients.
c. At 3-6 hours, there are 157 MI patients and 941 non MI patients. Please explain why there are more MI patients at 3-6 hours than at 1-3 hours? Please explain what happened to the missing 96 MI patients (253-157) and the missing 735 non MI patients (1676-941).
d. At 6-9 hours, there are 43 MI patients and 246 non MI patients. Please explain what happened to the missing 210 MI patients (253-43) and to the missing 1430 non MI patients (1676-246).

Beckman Coulter's Response (for b, c and d):

There are not missing patients. The differences in the numbers are the result of the aspects of the trial design discussed below.

General Comment Concerning Both Time from Admission and Time from Symptom Onset Data
Please refer to the following paragraph from Section 9.10.4.9 of the submission:

> Note: N's do not add to the total number of subjects due to serial draws - with samples from a single subject in multiple time intervals. If more than one draw was obtained for a particular subject within any specific time interval, the analysis included only one sample per subject per time interval. Thus, a single subject can appear in multiple time intervals but no more than once in each time interval. In addition, time from symptom onset was in some instances unavailable.

The analysis included only one sample per subject per time interval in order to meet statistical assumptions of independence of observations, and to prevent preferential weighting of frequently sampled subjects over subjects with few samples.

Response Concerning Time from Admission Data
The current standard of care for the majority of Non-MI subjects is to obtain 1-2 draws, per ED guidelines. The same is true for MI subjects (2 draws are common; current guidelines emphasize timely reperfusion therapy within 90 minutes). In the "troponin era," prolonged serial blood samples are no longer collected as done 15 years ago as this would potentially harm patients by

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preventing immediate intervention and does not reflect the current management of patients.

The clinical trial design discussed during pre-IDE discussions with FDA noted:

> A minimum of 3 blood draws within 24 hours of presentation is desirable (collected at presentation and at every standard-of-care follow-up draw). However, 2 blood draws are acceptable when immediate intervention is required, per standard-of-care, and a 3rd draw could not be obtained without delaying treatment. (Restricting the study to only those subjects with ≥3 samples would lead to selection bias by eliminating the majority of MI patients who receive timely reperfusion therapy per the American Heart Association's "Get With The Guidelines" recommendations.)

The Universal Definition of MI guidelines recommend a baseline draw and a second draw at 6-9 hours. Literature studies are now recommending an earlier draw prior to 6-9 hours in order to obtain an earlier MI diagnosis, but a consensus on timing has not yet been reached. In order to obtain a representative study population diagnosed and treated per current standard of care, some patient samples fell within the 1-3 hour window, some within the 3-6 hour window, and some within both windows. BEC's troponin I results are nearly identical for these time frames. These time frames could have been combined in the analysis, but we felt it was important to present data in systematic, regular intervals over time as it shows that BEC's troponin I performance is excellent very early on, and it addresses all current methods of patient management. Sites obtained study samples at all standard of care draws, and results were analyzed per the predefined time windows specified in the study protocol. More frequent and earlier samples are obtained in the ED when the physician is concerned with the patient's medical history or the results of the first draw, and we included these draws in the study analysis.

e. At less than 8 hours since symptom onset the total number of MI patients is 165 and the non MI patients is 993. Where are the missing 88 MI patients (253-165) and the missing 683 patients (1676-993)?

Beckman Coulter's Response:
These patients presented to the ED ≥8 hours after symptom onset. Therefore, all study samples for these patients are ≥8 hours after symptom onset.

The comments above for (b) (c) and (d) also apply here.

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f. At more than 8 hours after symptom onset, there are 159 MI patients and 1113 non MI patients. Where are the missing 94 MI patients (253-159)? Where are the missing 563 non MI patients (1676-1113)?

Beckman Coulter's Response:
Many of these patients presented to the ED <8 hours after symptom onset, and were sampled, treated or discharged before ≥8 hours had elapsed.

The comments above for (b) (c) and (d) also apply here.

Please contact me if you have any questions regarding the information in this response. I can be reached directly at 952-368-1142 or at my email address.

Regards,

Cindy McGuire
Senior Regulatory Specialist
Beckman Coulter
Chaska, MN 55318
cmcguire@beckman.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Monday, June 04, 2012 11:09 AM
To: Caposino, Paula
Cc: Chuck Willand; Scott T Cundy; Valynda Machen
Subject: RE: K121214 request for protocol clarification - part 2 - clinical analysis questions

Hello Dr. Caposino

Beckman Coulter will have the response to you by 3pm Eastern time, if not earlier, today.

Once again, I apologize for the delay.

Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

06/04/2012 08:19 AM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc Scott T Cundy <STCundy@beckman.com>, Chuck Willand <CWilland@beckman.com>, Valynda Machen <vmachen@beckman.com>
Subject RE: K121214 request for protocol clarification - part 2

Dear Cindy,
Thanks for the email. When can I expect your response?
Paula

From: Cindy McGuire [mailto:cmcguire@beckman.com]
Sent: Friday, June 01, 2012 5:34 PM
To: Caposino, Paula
Cc: Scott T Cundy; Chuck Willand; Valynda Machen
Subject: RE: K121214 request for protocol clarification - part 2

Hello Dr. Caposino,

I am contacting you to let you know that you can expect Beckman Coulter's response to your clinical analysis questions on Monday, June 4, 2012. We need some more time to get additional input from our clinical group to finalize our response.

I apologize that we did not meet you request date of today, June 1, 2012.

Regards,
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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05/31/2012 12:34 PM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc
Subject RE: K121214 request for protocol clarification - part 2

Thank you so much.

Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Friday, June 01, 2012 10:37 AM
To: Caposino, Paula
Cc: Scott T Cundy; Chuck Willand; Valynda Machen
Subject: RE: K121214 request for raw data - interference and cross-reactivity studies
Attachments: K121214 data request June 1 2012.pdf; IF Sub and Cross Reactants Raw Data.xls

Hello Dr, Caposino

Attached is the response from BEC for the raw data for the interference studies and the cross reactivity studies information you requested.

Please let me know if you have any questions.

I also wanted to confirm that you received the diskettes with the clinical data.

Thanks,
Cindy

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BECKMAN COULTER

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
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CDRH, OIVD, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

RE: K121214 request for raw data and protocol clarification

Dear Dr. Caposino,

As requested, Beckman Coulter is proving a response to your request below:
Do you think you can provide the raw data for the interference studies and the cross reactivity studies?

Beckman Coulter's response:
The raw data for the interference and analytical specificity studies (Study 8.8) and the cross-reactivity studies (Study 8.9) are attached to this e-mail message as an Excel file.

The interference and analytical specificity and cross-reactivity studies were based on CLSI EP7-A and were completed at each of three different temperature conditions (18°C, 28°C and normal laboratory conditions (NLC) which ranged from 21.8°C to 25.3°C). One lot of reagent packs was used. All substances were tested at each of the three temperature conditions. Each tab of the attached Excel workbook contains the data for the individual study performed at the particular temperature.

For the testing done at 18°C:
- 3 instruments were used (same three as 28°C testing),
- 4 total calibrations;
- testing took place on 11 different days (not consecutive)

For the testing done at NLC:
- 3 instruments were used (different instruments from those used for 18°C and 28°C testing),
- 3 total calibrations;
- testing took place on 11 different days (not consecutive)

For the testing done at 28°C:
- 3 instruments were used (same three as 18°C testing),
- 5 total calibrations;
- testing took place on 14 different days (not consecutive)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please contact me if you have any questions regarding the information in this response. I can be reached directly at 952-368-1142 or at my email address.

Regards,

Cindy McGuire
Senior Regulatory Specialist
Beckman Coulter
Chaska, MN 55318
cmcguire@beckman.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Thursday, May 31, 2012 1:33 PM
To: Caposino, Paula
Cc: Valynda Machen; Scott T Cundy; Chuck Willand
Subject: RE: K121214 request for protocol clarification - part 2

Hello Dr. Caposino,

I wanted to let you know that I am working with our clinical studies scientist to provide the answers to your questions. I will send you our response as soon as possible.

Thanks
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

05/31/2012 11:10 AM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc
Subject RE: K121214 request for protocol clarification - part 2

Dear Cindy,
Thank you for your continued help with this submission. While I wait for the clinical data, please provide the following information:

1. Adjudicator Panel Diagnosis: The adjudication panel diagnosed 253 MIs while the site diagnosed 171 MIs (20 of which were adjudicated as non MI). Please provide the following:
a. Did the adjudication panel review the same clinical information that the site panel reviewed? Did they have any additional/differing information?
b. Can you identify the sites at which the discordant diagnoses were found?
c. How many draws did these 102 patients provide?

2. Sensitivity and Specificity tables: While we understand that some patients diagnosed with MI may not have provided additional blood draws once they were diagnosed, we do not understand your sensitivity and specificity tables. Specifically, please provide the following information for the tables at the different blood draw time points (a-d) and for the tables at the different times since the onset of symptoms (e and f):
a. At baseline there are 1928 subjects listed (1675 + 253) instead of 1929. Please correct or clarify.
b. At 1-3 hours, there are 124 MI patients and 1014 non MI patients. Please explain what happened to the missing 132 MI patients (253-124) and the missing 662 (1676-1014) non MI patients.
c. At 3-6 hours, there are 157 MI patients and 941 non MI patients. Please explain why there are more MI patients at 3-6 hours than at 1-3 hours? Please explain what happened to the missing 96 MI

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patients (253-157) and the missing 735 non MI patients (1676-941).

d. At 6-9 hours, there are 43 MI patients and 246 non MI patients. Please explain what happened to the missing 210 MI patients (253-43) and to the missing 1430 non MI patients (1676-246).

e. At less than 8 hours since symptom onset the total number of MI patients is 165 and the non MI patients is 993. Where are the missing 88 MI patients (253-165) and the missing 683 patients (1676-993)?

f. At more than 8 hours after symptom onset, there are 159 MI patients and 1113 non MI patients. Where are the missing 94 MI patients (253-159)? Where are the missing 563 non MI patients (1676-1113)?

Please provide this information to me as soon as possible (preferably by the end of this week).

Thank you very much for your help.

Regards,

Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Wednesday, May 30, 2012 4:17 PM
To: Caposino, Paula
Cc: Kurtis R Bray; Scott T Cundy; Chuck Willand
Subject: Fw: K121214 request for protocol clarification - part 2

Hello Dr. Caposino,

I need to correct my statement below - I misspoke...

"Both the serum and the plasma results are provided for each sample." - Only the matrix comparison study samples include both serum and plasma results.

I apologize if this caused any confusion.

Thanks,
Cindy

----- Forwarded by Cindy McGuire/RD/US/BCI on 05/30/2012 03:11 PM -----

Cindy McGuire/RD/US/BCI

05/30/2012 03:02 PM

To "Caposino, Paula" <Paula.Caposino@fda.hhs.gov>
cc Kurtis R Bray/RD/US/BCI@BCI, Scott T Cundy/RD/US/BCI@BCI, Chuck Willand/EXT/US/BCI@BCI
Subject RE: FW: K121214 request for protocol clarification - part 2 Link

Hello Dr. Caposino

You are correct - the diskette I sent last week does not have the clinical trial data on it.

I will make copies of the clinical trial diskette and FedEx them to you today.

Both the serum and the plasma results are provided for each sample.

Let me know if there is anything else you need.

Thanks,
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

To 'Cindy McGuire' <cmcguire@beckman.com>
cc

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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05/30/2012 02:28 PM Subject RE: FW: K121214 request for protocol clarification - part 2

Hi Cindy,
Thanks for the quick response. Unfortunately, I never received that diskette and I don't think that data was included in the diskettes that you sent to me last week correct?
Thanks,
Paula

I would also appreciate the matrix comparison data from the pivotal study too.

Let me know how we can proceed.

From: Cindy McGuire [mailto:cmcguire@beckman.com]
Sent: Wednesday, May 30, 2012 3:20 PM
To: Caposino, Paula
Subject: RE: FW: K121214 request for protocol clarification - part 2

Hello Dr. Caposino,

The patient data for the pivotal trial was included with the hard copy submission on a diskette titled : Access AccuTnI on the Access 2 Immunoassay System Pivotal and Reference interval trial data sets.

Please let me know if you need another copy of this diskette or if the information you are looking for was not on that diskette.

Thanks,
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

05/30/2012 12:19 PM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc
Subject RE: FW: K121214 request for protocol clarification - part 2

Dear Cindy,
Thanks again for the email. One question, do you have access to the patient data for the pivotal trial? We need the AccuTnI assay results for each draw for each patient, the attending physicians' diagnosis and final diagnosis for each patient in the pivotal trial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Thanks, Paula

From: Cindy McGuire [mailto:cmcguire@beckman.com]
Sent: Wednesday, May 30, 2012 11:16 AM
To: Caposino, Paula
Cc: Scott T Cundy; Valynda Machen
Subject: RE: FW: K121214 request for protocol clarification - part 2

Hello Dr, Caposino

I will have the data for the interference and cross reactivity studies for you on Friday, June 1. Please let me know if this date is acceptable?

I was planning to provide the calibration frequency and study duration information as well. Please let me know if that is not needed.

Regards,
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

05/29/2012 01:48 PM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc
Subject RE: FW: K121214 request for protocol clarification - part 2

Dear Cindy,
Thank you for the information. Do you think you can provide the raw data for the interference studies and the cross reactivity studies?
Thank you very much.
Regards,
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Thursday, May 24, 2012 2:41 PM
To: Caposino, Paula
Cc: Chuck Willand; Scott T Cundy; Valynda Machen; Jennifer D Tibodeau
Subject: RE: FW: K121214 request for protocol clarification - part 2
Attachments: K121214 data request May 24 2012.pdf; 8.1 LoB raw data.xls; 8.2 LoD raw data.xls; 8.3 LoQ raw data.xls; 8.4 Precision raw data.xls; 8.5 Linearity raw data.xls; 8.10 Sample Matrix Access2 raw data.xls

Hello Dr. Caposino

The information for the analytical testing you needed to complete your review of K121214 is attached below.

This response contains the information you requested for question 2.

2. Please also provide the raw data for the limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies. For these studies, please also provide a protocol describing how long the instruments were equilibrate at each temperature. Also, please include a description of how you validated that each instrument had reached the assigned temperature. Please provide this information to me as soon as possible. Again, I prefer clearly labeled excel files if at all possible.
One more request, for item 2 (i.e. limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies), please also describe over how many days each experiment was performed.

Please contact me if you have any questions or additional requests.

Regards,
Cindy

The server made the following annotations

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Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIVD, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

RE: K121214 request for raw data and protocol clarification

Dear Dr. Caposino,

As requested, Beckman Coulter is providing a response to your request below:

2. *Please also provide the raw data for the limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies.*

   For these studies, please also provide a protocol describing how long the instruments were equilibrated at each temperature.

   Also, please include a description of how you validated that each instrument had reached the assigned temperature. Please provide this information to me as soon as possible. Again, I prefer clearly labeled excel files if at all possible.

   One more request, for item 2 (i.e. limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies), please also describe over how many days each experiment was performed.

Beckman Coulter's response:

2. The raw data for the limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies are attached to this e-mail message as individual Excel files.

   As stated in BEC's previous response dated May 22, 2012, there was not a separate protocol used for equilibrating the instrument at each temperature. Prior to beginning each temperature controlled study, each instrument was allowed to equilibrate a minimum of one hour. The equilibration instructions were part of the Verification Plan / Protocol.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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8.1 Limit of Blank Study

Temperature Equilibration

For the "Limit of Blank" 18°C study described in section 8.1.1, all runs were completed at 18°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Blank" normal laboratory conditions (NLC) study described in section 8.1.1, all runs were completed at the normal operating temperature of the laboratory between 18°C and 28°C so no equilibration time was necessary.

For the "Limit of Blank" 28°C study described in section 8.1.1, all runs were completed at 28°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Blank" multi-temperature study described in section 8.1.2, instruments were allowed to equilibrate a minimum of one hour per temperature set point, per the Verification Plan/Protocol.

Instrument Temperature Validation

For the "Limit of Blank" 18°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Blank" NLC study, ambient temperature was validated to be within the target range (between 18°C and 28°C) using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Blank" 28°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Blank" multi-temperature study, ambient temperature set points were validated to be within +/-2°C of the target set point using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set point.

Duration of Study and Calibration Frequency

The "Limit of Blank" study at 18°C described in section 8.1.1 was performed on three instruments, two reagent pack lots, and two calibrator lots over two days. The assay was calibrated for each individual run, and 12 runs were completed.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The "Limit of Blank" study at NLC described in section 8.1.1 was performed on three instruments, two reagent pack lots, and two calibrator lots over two days. The assay was calibrated for each individual run, and 12 runs were completed.
The "Limit of Blank study at 28°C described in section 8.1.1 was performed on three instruments, two reagent pack lots, and two calibrator lots over two days. The assay was calibrated for each individual run, and 12 runs were completed.

The "Limit of Blank" multi-temperature study described in section 8.1.2 was performed at six temperature set points (18°C, 20°C, 22°C, 24°C, 26°C, and 28°C). The study was performed on three instruments, two reagent pack lots, and two calibrator lots over three days. The assay was calibrated for each individual run, and 12 runs were completed (two runs per temperature).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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8.2 Limit of Detection Study

Temperature Equilibration

For the "Limit of Detection" 18°C study described in section 8.2.1, all runs were completed at 18°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Detection" NLC study described in section 8.2.1, all runs were completed at the normal operating temperature of the laboratory between 18°C and 28°C so no equilibration time was necessary.

For the "Limit of Detection" 28°C study described in section 8.2.1, all runs were completed at 28°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Detection" multi-temperature study described in section 8.2.2, instruments were allowed to equilibrate a minimum of one hour per temperature set point, per the Verification Plan/Protocol.

Instrument Temperature Validation

For the "Limit of Detection" 18°C study, ambient temperature setpoints were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Detection" NLC study, ambient temperature was validated to be within the target range (between 18°C and 28°C) using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Detection" 28°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Detection" multi-temperature study, ambient temperature set points were validated to be within +/-2°C of the target set point using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set point.

Duration of Study and Calibration Frequency

The "Limit of Detection" study at 18°C described in section 8.2.1 was performed on three instruments, two reagent pack lots, and two calibrator lots over two days. The assay was calibrated for each individual run, and 12 runs were completed.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The "Limit of Detection" study at NLC described in section 8.2.1 was performed on three instruments, two reagent pack lots, and two calibrator lots over two days. The assay was calibrated for each individual run, and 12 runs were completed.

The "Limit of Detection" study at 28°C described in section 8.2.1 was performed on three instruments, two reagent pack lots, and two calibrator lots over two days. The assay was calibrated for each individual run, and 12 runs were completed.

The "Limit of Detection" multi-temperature study described in section 8.2.2 was performed at six temperature set points (18°C, 20°C, 22°C, 24°C, 26°C, and 28°C). The study was performed on three instruments, two reagent pack lots, and two calibrator lots over three days. The assay was calibrated for each individual run, and 12 runs were completed (two runs per temperature).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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8.3 Limit of Quantitation Study

Temperature Equilibration

For the "Limit of Quantitation" 18°C study described in section 8.3.1, all runs were completed at 18°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Quantitation" NLC study described in section 8.3.1, all runs were completed at the normal operating temperature of the laboratory between 18°C and 28°C (actual achieved temperature range = 21°C to 25°C) so no equilibration time was necessary.

For the "Limit of Quantitation" 28°C study described in section 8.3.1, all runs were completed at 28°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Quantitation" multi-temperature study described in section 8.3.2, instruments were allowed to equilibrate a minimum of one hour per temperature set point, per the Verification Plan/Protocol.

Instrument Temperature Validation

For the "Limit of Quantitation" 18°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Quantitation" NLC study, ambient temperature was validated to be within the target range (between 18°C and 28°C) using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Quantitation" 28°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Quantitation" multi-temperature study, ambient temperature set points were validated to be within +/-2°C of the target set point using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set point.

Duration of Study and Calibration Frequency

The "Limit of Quantitation" 18°C study described in section 8.3.1 was performed at one temperature set point (18°C +/- 2°C) over 11 days on three instruments. Three reagent lots were used to perform this testing (one reagent lot per instrument). A single calibration curve was generated at 18°C +/-2°C prior to starting testing on each instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The "Limit of Quantitation" NLC study described in section 8.3.1 was performed over 10 days on three instruments. Three reagent lots were used to perform this testing (one reagent lot per instrument). A single calibration curve was generated prior to starting testing on each instrument.

The "Limit of Quantitation" 28°C study described in section 8.3.1 was performed at one temperature set point (28°C +/- 2°C) over 11 days on three instruments. Three reagent lots were used to perform this testing (one reagent lot per instrument). A single calibration curve was generated at 28°C +/-2°C prior to starting testing on each instrument.

The "Limit of Quantitation" multi-temperature study described in section 8.3.2 was performed at six temperature set points (18°C, 20°C, 22°C, 24°C, 26°C, and 28°C) over 12 days on three instruments. Three reagent lots were used to perform this testing (one reagent lot per instrument). A single calibration curve was generated at 24°C +/-2°C prior to starting testing on each instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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8.4 Precision Study

Temperature Equilibration

For the "Precision" 18°C study described in section 8.4.1, all runs were completed at 18°C +/- 2°C so no equilibration time between runs was necessary.

For the "Precision" NLC study described in section 8.4.1, all runs were completed at the normal operating temperature of the laboratory between 18°C and 28°C (actual achieved temperature range = 20°C to 24°C) so no equilibration time was necessary.

For the "Precision" 28°C study described in section 8.4.1, all runs were completed at 28°C +/- 2°C so no equilibration time between runs was necessary.

For the "Precision" multi-temperature study described in section 8.4.2, instruments were allowed to equilibrate a minimum of one hour per temperature set point, per the Verification Plan/Protocol.

Instrument Temperature Validation

For the "Precision" 18°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Precision" NLC study, ambient temperature was validated to be within the target range (between 18°C and 28°C) using a calibrated temperature recorder placed at each instrument prior to initiation of testing for each run.

For the "Precision" 28°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Precision" multi-temperature study, ambient temperature set points were validated to be within +/-2°C of the target set point using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set point.

Duration of Study and Calibration Frequency

The "Precision" 18°C study described in section 8.4.1 was performed at one temperature set point (18°C +/- 2°C) over 13 days on one instrument. One reagent lot was used to perform this testing. A single calibration curve was generated at 18°C +/-2°C prior to starting testing.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The "Precision" NLC study described in section 8.4.1 was performed over 20 days (2 shifts/day) on one instrument. One reagent lot was used to perform this testing. A single calibration curve was generated prior to starting testing.

The "Precision" 28°C study described in section 8.4.1 was performed at one temperature set point (28°C +/- 2°C) over 13 days on one instrument. One reagent lot was used to perform this testing. A single calibration curve was generated at 18°C +/-2°C prior to starting testing.

The "Precision" multi-temperature study described in section 8.4.2 was performed at six temperature set points (18°C, 20°C, 22°C, 24°C, 26°C, and 28°C) over 12 days on one instrument (two days per temperature). One reagent lot was used to perform this testing. A single calibration curve was generated at 24°C +/-2°C prior to starting testing.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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8.5 Linearity Study

Temperature Equilibration

For the "Linearity" 18°C study described in section 8.5, all runs were completed at 18°C +/- 2°C so no equilibration time between runs was necessary.

For the "Limit of Quantitation" NLC study described in section 8.5, all runs were completed at the normal operating temperature of the laboratory between 18°C and 28°C (actual achieved temperature range = 22°C to 24°C) so no equilibration time was necessary.

For the "Linearity" 28°C study described in section 8.5, all runs were completed at 28°C +/- 2°C so no equilibration time between runs was necessary.

Instrument Temperature Validation

For the "Linearity" 18°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Limit of Quantitation" NLC study, ambient temperature was validated to be within the target range (between 18°C and 28°C) using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

For the "Linearity" 28°C study, ambient temperature set points were validated to be within +/- 2°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing for each run.

Duration of Study and Calibration Frequency

The "Linearity" 18°C study described in section 8.5 was performed at one temperature set point (18°C +/- 2°C) over two days on two instruments. Two reagent lots were used to perform this testing. A single calibration curve was generated at 18°C +/-2°C on each instrument and reagent pack lot prior to starting testing.

The "Linearity" NLC study described in section 8.5 was performed over two days on two instruments. Two reagent lots were used to perform this testing. A single calibration curve was generated on each instrument and reagent pack lot prior to starting testing.

The "Linearity" 28°C study described in section 8.5 was performed at one temperature set point (28°C +/- 2°C) over one day on two instruments. Two reagent lots were used to perform this testing. A single calibration curve was generated at 28°C +/-2°C on each instrument and reagent pack lot prior to starting testing.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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8.10 Sample Matrix Study

Temperature Equilibration

For the "Sample Matrix Comparison" study described in section 8.10, instruments were allowed to equilibrate a minimum of one hour per temperature set point, per the Verification Plan/Protocol.

Instrument Temperature Validation

For the "Sample Matrix Comparison" study, ambient temperature set points were validated to be within +/-2°C of the target set point using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set point.

Duration of Study and Calibration Frequency

The "Sample Matrix Comparison" study described in section 8.10 was performed at three temperature set points (18°C, 23°C, and 28°C) over three days (one temperature per day) on two instruments. One reagent lot was used to perform this testing. One calibration curve was generated per instrument at each of the three temperature set points.

Please contact me if you have any questions regarding the information in this response. I can be reached directly at 952-368-1142 or at my email address.

Regards,

Cindy McGuire
Senior Regulatory Specialist
Beckman Coulter
Chaska, MN 55318
cmcguire@beckman.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Tuesday, May 22, 2012 4:35 PM
To: Caposino, Paula
Cc: Valynda Machen; Scott T Cundy
Subject: Fw: K121214 request for protocol clarification
Attachments: K121214 calibration frequency information May 22 2012.doc

Hello Dr. Caposino,

Attached is the response from BEC for the calibration frequency information you requested today. Please let me know if you have any questions.

I have also sent 2 additional CDs with the K121214 submission copied to them. They were sent FedEx to arrive tomorrow morning. The tracking number, if you should need it, is 8771 1858 1531.

Thanks,
Cindy

----- Forwarded by Cindy McGuire/RD/US/BCI on 05/22/2012 03:14 PM ----

Cindy McGuire/RD/US/BCI

05/22/2012 11:40 AM

To "Caposino, Paula" <Paula.Caposino@fda.hhs.gov>
cc Valynda Machen/RD/US/BCI@BCI, Scott T Cundy/RD/US/BCI@BCI
Subject RE: FW: K121214 request for protocol clarification Link

Hi Dr. Caposino,

I will gather the calibration frequency information for the 8.12, 8.13 and 8.14 studies and send you that response this afternoon.

We will also include the calibration frequency information for the other studies as part of Thursday's response.

Thanks!
Cindy

"Caposino, Paula" <Paula.Caposino@fda.hhs.gov>

05/22/2012 11:18 AM

To 'Cindy McGuire' <cmcguire@beckman.com>
cc
Subject RE: FW: K121214 request for protocol clarification

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Dear Cindy,
Thank you very much for the information. One more question, can you please describe the calibration frequency (i.e. calibration curve generated with each run, a calibration curve generated for the experiment, etc.).
Thank you again,
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIVD, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

RE: K121214 request for calibration frequency information

Dear Dr. Caposino,

As requested, Beckman Coulter is providing a response to your request below:

Please describe the calibration frequency (i.e. calibration curve generated with each run, a calibration curve generated for the experiment, etc.).

Beckman Coulter's response:
The calibration frequencies for the Thermal Sensitivity experiments (8.12, 8.13 and 8.14) are described below.

8.12 Thermal Sensitivity – Robustness
The study was run at six ambient temperatures. Two instruments were used for this testing. On each instrument, a calibration curve was established at each of the six temperature conditions. In total, 12 calibrations were generated during this study.

8.13 Thermal Sensitivity – Impact on Low Dose Concordance / Agreement
The study was run at six ambient temperatures. Two instruments and two reagent pack lots were used for this testing (one reagent pack lot per instrument). On each instrument, a single calibration at 24°C ± 2°C was established prior to testing initiation. In total, two calibrations were generated during this study.

8.14 Thermal Sensitivity – Impact on Cross-Temperature Method Comparison
This study was run at three ambient temperatures. Two instruments were used for this testing. On each instrument, a calibration curve was established at each of the three temperatures. In total, six calibrations were generated during this study.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please contact me if you have any questions regarding the information in this response. I can be reached directly at 952-368-1142 or at my email address.

Regards,

Cindy McGuire
Senior Regulatory Specialist
Beckman Coulter
Chaska, MN 55318
cmcguire@beckman.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Tuesday, May 22, 2012 12:14 PM
To: Caposino, Paula
Cc: Chuck Willand; Scott T Cundy; Valynda Machen; Jennifer D Tibodeau
Subject: RE: FW: K121214 request for protocol clarification
Attachments: K121214 data request May 22 2012.pdf; 8.12 Thermal Sensitivity-Robustness Access2 raw data v2.xls; 8.13 Concordance Agreement Access2 raw data v2.xls; 8.14 Cross-Temp MC Access2 raw data v2.xls

Hello Dr. Caposino,

As requested the information you needed to complete your review of K121214 is attached below.

This response contains the information for question 1 :
1. Thermal Sensitivity Robustness Studies: Please provide the following to me by Tuesday morning.
a. Please provide the raw data for all of these studies (8.12, 8.13, 8.14). I prefer clearly labeled excel files if at all possible.
b. For these studies, please also provide a protocol describing how long the instruments were equilibrate at each temperature. Also, please include a description of how you validated that each instrument had reached the assigned temperature.
c. Please describe over how many days was each study performed.

Beckman Coulter will submit the response for question 2 on Thursday, May 24.
2. Please also provide the raw data for the limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies. For these studies, please also provide a protocol describing how long the instruments were equilibrate at each temperature. Also, please include a description of how you validated that each instrument had reached the assigned temperature. Please provide this information to me as soon as possible. Again, I prefer clearly labeled excel files if at all possible.
One more request, for item 2 (i.e. limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies), please also describe over how many days each experiment was performed.

Regards,
Cindy

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

Paula Velasco Caposino, Ph.D.
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10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

RE: K121214 request for raw data and protocol clarification

Dear Dr. Caposino,

As requested, Beckman Coulter is providing a response to your request below:

1. Thermal Sensitivity Robustness Studies: Please provide the following to me by Tuesday morning.

a. Please provide the raw data for all of these studies (8.12, 8.13, 8.14). I prefer clearly labeled Excel files if at all possible.

b. For these studies, please also provide a protocol describing how long the instruments were equilibrated at each temperature. Also, please include a description of how you validated that each instrument had reached the assigned temperature.

c. Please describe over how many days was each study performed.

Beckman Coulter's response:

1. In regard to the Thermal Sensitivity Robustness Studies:
   a. The raw data for each of these studies (8.12, 8.13, and 8.14) are attached to this e-mail message as individual Excel files.
   b. There was not a separate protocol used for equilibrating the instrument at each temperature. The equilibration instructions were part of our Verification Plan / Protocol. Specifically:
      - Between ambient set-points during a study, at least 60 minutes will be allowed to let the room equilibrate.
      - Ambient temperature will be obtained by using a calibrated thermometer placed on top of each individual instrument (the tip of the thermometer should not touch the instrument so that air temperature is being measured). On Access 2 the thermometer should be placed in the center of the top cover. Ambient temperature data will be handled as follows:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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- Before each run for an individual study, the ambient temperature will be recorded and the temperature must be within the stated tolerance for the study

The one hour equilibration time is to let the ambient (air) temperature achieve the new set temperature, and this is verified by taking the ambient temperature at the instrument prior to starting the next run. The ambient temperature is being used in the AccuTnI verification testing since this is the environmental factor that laboratories have control over, and the thermal algorithm was implemented in order to account for shifts in ambient temperature. There is no specific instrument equilibration that is being accounted for in the one-hour timeframe.

For studies 8.12 "Thermal Sensitivity – Robustness," ambient temperature set points were validated to be within +/-1°C of the target using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set point.

For studies 8.13 "Thermal Sensitivity - Impact on Low Dose Concordance/Agreement" and 8.14 "Thermal Sensitivity - Impact on Cross-Temperature Method Comparison," ambient temperature set points were validated to be within +/-2°C of the target set point using a calibrated thermometer placed at each instrument prior to initiation of testing at each ambient temperature set-point.

c. The number of days it took to complete each study was:
The "Thermal Sensitivity - Robustness" study described in section 8.12 was performed at six temperature set points (16°C, 19°C, 22°C, 25°C, 27°C, and 30°C) over two days (three temperatures per day) on two instruments. One reagent lot was used to perform this testing.

The "Thermal Sensitivity - Impact on Low Dose Concordance/Agreement" study described in section 8.13 was performed at six temperature set points (18°C, 20°C, 22°C, 24°C, 26°C, and 28°C) over six days (one temperature per day) on two instruments. Two reagent lots were used to perform this testing (one reagent lot per instrument).

The "Thermal Sensitivity - Impact on Cross-Temperature Method Comparison" study described in section 8.14 was performed at three temperature set points (18°C, 23°C, and 28°C) over three days (one temperature per day) on two instruments. One reagent lot was used to perform this testing.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please contact me if you have any questions regarding the information in this response. I can be reached directly at 952-368-1142 or at my email address.

Regards,

Cindy McGuire
Senior Regulatory Specialist
Beckman Coulter
Chaska, MN 55318
cmcguire@beckman.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Caposino, Paula

From: Cindy McGuire [cmcguire@beckman.com]
Sent: Monday, May 21, 2012 11:51 AM
To: Caposino, Paula
Cc: 'Valynda Machen'; Scott T Cundy
Subject: Re: K121214 request for raw data and protocol clarification

Hello Dr. Caposino,

I wanted to confirm with you that Beckman Coulter will have the response for question 1 by tomorrow morning (Tuesday, May 22).

1. Thermal Sensitivity Robustness Studies: Please provide the following to me by Tuesday morning.

a. Please provide the raw data for all of these studies (8.12, 8.13, 8.14). I prefer clearly labeled excel files if at all possible.
b. For these studies, please also provide a protocol describing how long the instruments were equilibrate at each temperature. Also, please include a description of how you validated that each instrument had reached the assigned temperature.
c. Please describe over how many days was each study performed.

I would like to request an extension to Thursday morning (May 24) for the response to question 2. I apologize for they delay. I overlooked the fact that this response requires the compilation of 20 studies and I committed to the Tuesday morning date prior to speaking with my development scientist. Please let me know if Thursday morning would be acceptable for you.

2. Please also provide the raw data for the limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies. For these studies, please also provide a protocol describing how long the instruments were equilibrate at each temperature. Also, please include a description of how you validated that each instrument had reached the assigned temperature. Please provide this information to me as soon as possible. Again, I prefer clearly labeled excel files if at all possible.

One more request, for item 2 (i.e. limit of blank, limit of detection, limit of quantitation, precision, linearity, and sample matrix comparison studies), please also describe over how many days each experiment was performed.

Thank-you,

Cindy McGuire
Senior Regulatory Specialist
Beckman Coulter
Chaska MN 55318
952.368.1142

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

April 23, 2012

BECKMAN COULTER, INC.
1000 LAKE HAZELTINE DR.
CHASKA, MINNESOTA 55318-1084
ATTN: VALYNDA MACHEN

510k Number: K121214
Received: 4/23/2012
Product: ACCESS ACCUTNL REAGENT AND CAL

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act(Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On May 21, 2004, FDA issued a Guidance for Industry and FDA Staff entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment". The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. Please review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm.

In future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf) accompany 510(k)/HDE/PMA submissions. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

You should be familiar with the regulatory requirements for medical device available at Device Advice http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm". If you have other procedural questions, or want information on how to check on the status of your submission, please contact DSMICA at (301)796-7100 or its toll-free number (800)638-2041, or at their Internet address http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm or the 510k staff at (301)796-5640 .

Sincerely,

510(k) Staff

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Grayson, Giovanna *

From: Microsoft Outlook
To: 'vmachen@beckman.com'
Sent: Monday, April 23, 2012 11:24 AM
Subject: Relayed: ack letter

Delivery to these recipients or distribution lists is complete, but delivery notification was not sent by the destination:

'vmachen@beckman.com'

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Subject: ack letter
Attachments: image002.png

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

April 23, 2012
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CHASKA, MINNESOTA 55318-1084
ATTN: VALYNDA MACHEN

510k Number: K121214
Received: 4/23/2012
Product: ACCESS ACCUTNL REAGENT AND CAL

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Sincerely,

510(k) Staff

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K121214

FDA CDRH DMC
APR 23 2012
Received K24

April 20, 2012

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

SUBJECT: 510(k) Premarket Notification for
Access® AccuTnI on the Access 2 Immunoassay Systems

To Whom It May Concern:

Beckman Coulter, Inc. is submitting this 510(k) Premarket Notification for Access® AccuTnI on the Access 2 Immunoassay Systems. The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System. The Access 2 System is an in vitro diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

This 510(k) Premarket Notification contains the administrative information, device description, analytical performance data and the results of the prospective clinical study.

On May 20, 2010 FDA acknowledged receipt of pre-original investigational device exemption submission (Pre-IDE) I100255. A supplement to this Pre-IDE was submitted on May 19, 2011 (I100255/S002). The information contained in this notification is consistent with the information presented to FDA in the Pre-IDE and the supplement.

Clinical studies of the above device were initiated (first study subject enrolled at a clinical site) on September 16, 2010 and were not conducted under an approved

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investigational device exemption. The subject of this submission, Access AccuTnI, is exempt from 21 CFR Part 812 as described in Part 812.2 (c) (3). Beckman Coulter did conduct this clinical investigation under the standards of Good Clinical Practice, including training of all clinical investigators prior to study initiation, monitoring throughout the course of clinical investigations, and study close-outs with 100% review of the clinical data.

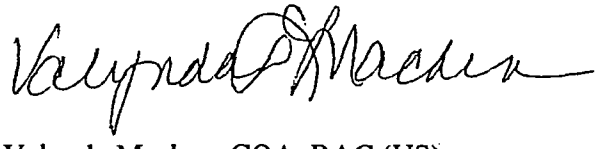
Access AccuTnI on the Access 2 Immunoassay Systems is manufactured by Beckman Coulter, Inc. at one manufacturing facility located at 1000 Lake Hazeltine Drive in Chaska, MN 55318.

In conformance with the National Environmental Policy Act, this 510(k) includes a claim for categorical exclusion.

The existence of this 510(k) and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed.

If there are questions regarding this submission, I may be contacted by telephone at (952) 368-1383, by fax at (952) 368-7610, or by e-mail at vmachen@beckman.com.

Sincerely,



Valynda Machen, CQA, RAC (US)
Group Manager, Regulatory Affairs

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access® AccuTnI on the Access 2 Immunoassay Systems

510(k) Premarket Notification

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318

April 20, 2012

Questions? Contact FDA/CDRH/OCE/DIB at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table of Contents

1.0 ADMINISTRATIVE 1-1

1.1. MEDICAL DEVICE USER FEE COVER SHEET 1-1
1.2. CDRH PREMARKET REVIEW SUBMISSION COVER SHEET 1-3
1.3. REQUIRED ELEMENTS CHECKLIST 1-9
1.4. INDICATIONS FOR USE STATEMENT 1-10
1.5. TRUTHFUL AND ACCURATE STATEMENT 1-13
1.6. 510(K) SUMMARY 1-14
1.7. FINANCIAL DISCLOSURE STATEMENT 1-19
1.8. CLASS III PRODUCT SUMMARY AND CERTIFICATION 1-20

2.0 INTENDED USE / INDICATIONS FOR USE 2-1

3.0 EXECUTIVE SUMMARY 3-1

3.1. BACKGROUND 3-1
3.2. DEVICE DESCRIPTION 3-2
3.3. SUBSTANTIAL EQUIVALENCE 3-3
3.4. PERFORMANCE TESTING 3-3
3.5. CONCLUSION 3-5

4.0 DEVICE DESCRIPTION 4-1

4.1. REAGENT KIT 4-2
4.2. CALIBRATOR KIT 4-3
4.3. SUBSTRATE 4-3
4.4. WASH BUFFER 4-3
4.5. ACCESS 2 IMMUNOASSAY SYSTEM 4-4

5.0 SUBSTANTIAL EQUIVALENCE DISCUSSION 5-1

6.0 SYSTEM SOFTWARE 6-1

6.1. LEVEL OF CONCERN 6-1
6.2. SOFTWARE DESCRIPTION 6-2
6.2.1. Introduction 6-2
6.2.2. Thermal Algorithm and Assay Result Suppression 6-3
6.2.3. "U" Command 6-5
6.2.4. Device Features Controlled by Software 6-5
6.2.5. Operational Environment 6-6
6.2.5.1. Hardware Platform 6-6
6.2.5.2. Programming Languages and Operating System 6-7
6.3. RISK MANAGEMENT 6-8
6.3.1. Risk Management Plan 6-8
6.3.2. Work Item Evaluation and Risk Assessment 6-9
6.3.3. Access 2 3.3 System Software Change Risk Assessment 6-10
6.3.4. Access 2 System Risk Assessment 6-11
6.3.5. Risk Management Review 6-11
6.3.6. Risk Management Report and Conclusion 6-12
6.4. SOFTWARE REQUIREMENTS SPECIFICATION 6-12
6.5. ARCHITECTURE DESIGN 6-13
6.6. SOFTWARE DESIGN SPECIFICATION 6-13
6.7. TRACEABILITY 6-13

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6.8. SOFTWARE DEVELOPMENT PROCESS 6-14
6.8.1. Thermal Control Algorithm Design and Development Plan *6-15*
6.8.2. Thermal System Software Design and Development Plan *6-15*
6.8.3. Access 2 Software Development Plan *6-16*
6.8.4. Software Configuration Management Plan *6-17*
6.8.5. Access 2 3.3 Software Risk Management Plan *6-17*
6.8.6. Access 2 3.3 Software Testing and Software Validation Plan *6-18*
6.9. SOFTWARE VERIFICATION AND VALIDATION TESTING 6-18
6.9.1. Test Objectives *6-18*
6.9.2. Software Test Items *6-18*
6.9.3. Test Documents *6-19*
6.9.4. Overview of Testing *6-19*
6.9.5. Unit Test *6-21*
6.9.6. Integration Test *6-21*
6.9.7. Change Point Analysis *6-22*
6.9.8. Software System Verification Testing *6-22*
6.9.9. System Integration Software Testing- IUO Build *6-27*
6.9.9.1. Testing Description 6-28
6.9.9.2. Testing Results 6-29
6.9.10. System Integration Software Testing- IVD Build *6-30*
6.9.11. Software System Level Test *6-32*
6.9.12. Software Validation *6-34*
6.9.13. Conclusion *6-37*
6.10. SOFTWARE REVISION HISTORY 6-38
6.11. UNRESOLVED ANOMALIES 6-43

7.0 HARDWARE 7-1

7.1. HARDWARE DESIGN CHANGES 7-1
7.2. HARDWARE VERIFICATION 7-1
7.2.1. Verification of the Temperature Measurement Accuracy of ±1.0 °C *7-1*
7.2.2. Verification of the Instrument Operating Temperature Range of 18°C to 28°C (ambient) and 18°C to 36°C (instrument case temperature) *7-2*

8.0 ANALYTICAL PERFORMANCE 8-1

8.1. LIMIT OF BLANK (LOB) 8-5
8.1.1. Standardized LoB Study *8-5*
8.1.2. Multi-Temperature Study (Thermal Sensitivity – Impact on LoB) *8-6*
8.1.3. Cross-Temperature LoB Analysis *8-7*
8.1.4. Limit of Blank Conclusion *8-8*
8.2. LIMIT OF DETECTION (LOD) 8-9
8.2.1. Standardized LoD Study *8-9*
8.2.2. Multi-Temperature Study (Thermal Sensitivity – Impact on LoD) *8-10*
8.2.3. Cross-Temperature LoD Analysis *8-12*
8.2.4. Limit of Detection Conclusion *8-14*
8.3. LIMIT OF QUANTITATION (LOQ) 8-14
8.3.1. Standardized LoQ Study *8-14*
8.3.2. Multi-Temperature Study (Thermal Sensitivity – Impact on LoQ) *8-16*
8.3.3. Cross-Temperature LoQ Analysis *8-18*
8.3.4. Limit of Quantitation Conclusion *8-21*
8.4. PRECISION 8-21
8.4.1. Standardized Total Precision *8-22*
8.4.2. Multi-temperature Study (Thermal Sensitivity – Impact on Precision) *8-24*
8.4.3. Cross-temperature Precision Analysis *8-25*

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8.4.4. Precision Conclusion *8-27*
8.5. LINEARITY 8-27
8.5.1. Overall Linearity Conclusion *8-30*
8.6. HIGH DOSE HOOK EFFECT 8-30
8.7. STABILITY 8-32
8.7.1. Reagent Pack Real Time Stability *8-34*
8.7.2. Reagent Open Pack Stability *8-37*
8.7.3. Stored Calibration Curve Stability *8-40*
8.7.4. Calibrator Real Time Stability *8-44*
8.7.5. Calibrator Open Vial Stability *8-49*
8.8. INTERFERENCE AND ANALYTICAL SPECIFICITY 8-51
8.9. CROSS-REACTIVITY 8-55
8.10. SAMPLE MATRIX COMPARISON 8-56
8.11. HAMA / HETEROPHILE 8-59
8.12. THERMAL SENSITIVITY – ROBUSTNESS 8-61
8.13. THERMAL SENSITIVITY – IMPACT ON LOW DOSE CONCORDANCE/AGREEMENT 8-62
8.14. THERMAL SENSITIVITY – IMPACT ON CROSS-TEMPERATURE METHOD COMPARISON 8-65
8.15. SAMPLE HANDLING 8-68
8.16. ANALYTICAL PERFORMANCE CONCLUSION 8-69

9.0 CLINICAL TRIAL 9-1

9.1. CLINICAL TRIALS TABLE OF CONTENTS 9-2
9.2. OBJECTIVES AND OVERVIEW OF THE CLINICAL TRIALS 9-5
9.3. INTENDED USE 9-8
9.4. INSTITUTIONAL REVIEW BOARD (IRB) AND INFORMED CONSENT 9-8
9.5. DATA QUALITY ASSURANCE 9-8
9.6. BLOOD COLLECTION, SPECIMEN TYPES, PROCESSING, STORAGE 9-9
9.7. LABORATORY TESTING 9-10
9.7.1. Precision *9-10*
9.7.2. Daily Quality Control (QC) Testing Over Time *9-11*
9.8. REFERENCE INTERVAL TRIAL 9-14
9.8.1. Study Objective *9-14*
9.8.2. Study Sites / Investigators *9-14*
9.8.3. Study Design *9-14*
9.8.3.1. Study Duration 9-15
9.8.3.2. Subject Inclusion Criteria 9-15
9.8.3.3. Subject Exclusion Criteria 9-15
9.8.3.4. Statistical Analysis Methods 9-16
9.8.3.5. Specimen Testing Methods 9-16
9.8.4. Results *9-17*
9.8.4.1. Number of Subjects 9-17
9.8.4.2. Demographic and Clinical Characteristics 9-18
9.8.4.3. Distribution of Troponin Values by Age and Sex 9-19
9.8.4.4. AccuTnI 99th Percentile Upper Reference Limit (URL) 9-21
9.8.5. Reference Interval Trial: Summary and Conclusions *9-21*
9.9. FEASIBILITY EFFICACY TRIAL 9-22
9.9.1. Study Objectives *9-22*
9.9.2. Study Site / Investigator *9-22*
9.9.3. Study Design *9-22*
9.9.3.1. Study Duration 9-23
9.9.3.2. Subject Inclusion Criteria 9-23
9.9.3.3. Subject Exclusion Criteria 9-23
9.9.3.4. Clinical Endpoint, Universal Definition of Myocardial Infarction (MI) 9-23
9.9.3.5. Adjudication of Clinical Endpoint 9-24

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9.9.3.6. Statistical Analysis Methods....9-24
9.9.3.7. Specimen Testing Methods....9-25
9.9.4. Results....9-25
9.9.4.1. Number of Subjects by Diagnosis....9-25
9.9.4.2. Demographic and Clinical Characteristics....9-26
9.9.4.3. Distribution of Troponin Values by Diagnosis....9-27
9.9.4.4. Diagnostic Sensitivity and Specificity Results at Baseline, 1-3 Hours, 3-6 Hours, and 6-9 Hours After Admission....9-28
9.9.4.5. Diagnostic Sensitivity and Specificity by Time After Symptom Onset....9-30
9.9.4.5.1. Results <8 Hours After Symptom Onset....9-31
9.9.4.5.2. Results ≥8 Hours After Symptom Onset....9-32
9.9.4.6. Determination of Cutoff Yielding 95% Diagnostic Sensitivity....9-33
9.9.5. Feasibility Efficacy Trial: Summary and Conclusions....9-35
9.10. PIVOTAL EFFICACY TRIAL....9-36
9.10.1. Study Objectives....9-36
9.10.2. Study Sites / Investigators....9-37
9.10.3. Study Design....9-39
9.10.3.1. Study Duration....9-39
9.10.3.2. Subject Inclusion Criteria....9-39
9.10.3.3. Subject Exclusion Criteria....9-40
9.10.3.4. Clinical Endpoint, Universal Definition of Myocardial Infarction (MI)....9-40
9.10.3.5. Adjudication of Clinical Endpoint....9-40
9.10.3.6. Statistical Sample Size Assumptions and Calculations....9-41
9.10.3.7. Statistical Analysis Methods....9-42
9.10.3.8. Pooling of Data Across Sites....9-42
9.10.3.9. Specimen Testing Methods....9-43
9.10.4. Results....9-44
9.10.4.1. Comparison of Investigational Site and Independent Central Adjudication Panel Diagnosis....9-44
9.10.4.2. Number of Subjects by Site and Diagnosis....9-45
9.10.4.3. MI Incidence by Site....9-46
9.10.4.4. Demographic and Clinical Characteristics, Overall Study Population....9-48
9.10.4.5. Demographic and Clinical Characteristics by Diagnosis....9-49
9.10.4.6. Distribution of Troponin Values By Diagnosis....9-52
9.10.4.7. Distribution of Troponin Values By Diagnosis and Sex....9-52
9.10.4.8. Distribution of Troponin Values By Diagnosis and Age....9-53
9.10.4.9. Diagnostic Sensitivity and Specificity by Time After Symptom Onset....9-54
9.10.4.9.1. Results <8 Hours After Symptom Onset....9-56
9.10.4.9.2. Results ≥8 Hours After Symptom Onset....9-58
9.10.4.9.3. Results by Site / Poolability of Investigational Site Data....9-60
9.10.4.9.4. Results by Sex....9-61
9.10.4.9.5. Results by Age....9-63
9.10.4.9.6. Diagnostic Sensitivity and Specificity by Time After Symptom Onset: Summary and Conclusions 9-64
9.10.4.10....Diagnostic Sensitivity and Specificity by Time After Admission....9-66
9.10.4.10.1. Results at Baseline, 1-3 Hours, 3-6 Hours, 6-9 Hours After Admission....9-68
9.10.4.10.2. Diagnostic Sensitivity and Specificity by Time After Admission: Summary and Conclusions 9-71
9.10.4.11....Positive Predictive Value (PPV) and Negative Predictive Value (NPV)....9-73
9.10.4.11.1. PPV and NPV Results by Time After Symptom Onset....9-74
9.10.4.11.2. PPV and NPV Results by Time After Admission....9-75
9.10.4.11.3. PPV and NPV: Summary and Conclusions....9-76
9.10.4.12....Non-MI Patients with Elevated TnI Values (Myocardial Damage)....9-78
9.10.4.12.1. Results 9-78
9.10.4.12.2. Non-MI Patients with Elevated TnI Values (Myocardial Damage): Summary and Conclusions 9-80

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9.10.5. Pivotal Efficacy Trial: Summary and Conclusions *9-81*
9.11. METHOD COMPARISON TO PREDICATE 9-83
9.11.1. Study Objectives *9-83*
9.11.2. Study Sites / Investigators *9-83*
9.11.3. Study Design *9-83*
9.11.3.1. Subject Inclusion and Exclusion Criteria 9-83
9.11.3.2. Sample Size Rationale and Statistical Analysis Methods 9-83
9.11.3.3. Specimen Testing Methods 9-84
9.11.4. Results *9-85*
9.11.4.1. Number of Samples 9-85
9.11.4.2. Regression Analysis and Correlation Coefficient 9-86
9.11.4.3. Concordance (% agreement) 9-87
9.11.4.4. Diagnostic Sensitivity and Specificity 9-88
9.11.4.5. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) 9-90
9.11.5. Method Comparison to Predicate: Summary and Conclusions *9-92*
9.12. SAMPLE MATRIX COMPARISON (LITHIUM HEPARIN PLASMA, SERUM) 9-94
9.12.1. Study Objectives *9-94*
9.12.2. Study Sites / Investigators *9-94*
9.12.3. Study Design *9-94*
9.12.3.1. Subject Inclusion and Exclusion Criteria 9-94
9.12.3.2. Sample Size Rationale and Statistical Analysis Methods 9-94
9.12.3.3. Specimen Testing Methods 9-95
9.12.4. Results *9-96*
9.12.4.1. Number of Samples 9-96
9.12.4.2. Regression Analysis and Correlation Coefficient 9-96
9.12.5. Sample Matrix Comparison: Summary and Conclusions *9-96*
9.13. ATTACHMENT I: BIBLIOGRAPHY 9-97
9.14. ATTACHMENT II: INVESTIGATIONAL SITES (SUBJECT ENROLLMENT) 9-99
9.15. ATTACHMENT III : SPECIMEN TESTING SITES (LABORATORIES) 9-103
9.16. ATTACHMENT IV: INDEPENDENT CENTRAL ADJUDICATION PANEL MEMBERS 9-104
9.17. ATTACHMENT V: FORM FDA 3454 "CERTIFICATION: FINANCIAL INTEREST AND ARRANGEMENTS OF CLINICAL INVESTIGATORS" 9-105
9.18. ATTACHMENT VI: PIVOTAL EFFICACY TRIAL PROTOCOL AND CASE REPORT FORMS 9-113
9.19. ATTACHMENT VII: CERTIFICATION OF COMPLIANCE WITH REQUIREMENTS OF CLINICALTRIALS.GOVDATA BANK 9-137

10.0 SUPPLEMENTAL INFORMATION – FIELD EFFECTIVENESS STUDY 10-1

10.1. INTRODUCTION 10-1
10.2. INTERNAL STUDY 10-1
10.3. EXTERNAL STUDY - CLINICAL TRIAL PRECISION 10-4
10.4. OVERALL CONCLUSION– FIELD EFFECTIVENESS STUDY 10-8

11.0 PROPOSED LABELING 11-1

12.0 OVERALL CONCLUSION 12-1

13.0 CLIA REQUEST 13-1

Tables

Table 1: Similarities between the Access AccuTnI Reagent and Calibrator and the Predicate 5-1
Table 2: Differences between the Access AccuTnI Reagent and Calibrator and the Predicate 5-2
Table 3: Similarities between the Access 2 Immunoassay System and the Predicate 5-3
Table 4: Differences between the Access 2 Immunoassay System and the Predicate 5-4
Table 5: Level of Concern 6-1

Questions? Contact FDA/CDRH/OCE/DIB at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 6: Device Features Controlled by Software 6-6
Table 7: Off-the-Shelf Components 6-7
Table 8: Concern Code Categories 6-9
Table 9: Software Requirements Specifications 6-13
Table 10: Development Plans 6-15
Table 11: Software Test and Validation Documents 6-19
Table 12: Software System Verification Testing 6-23
Table 13: Results of Comparison Testing- IUO 6-29
Table 14: Results of Comparison Testing- IVD 6-31
Table 15: System Level Testing Assays 6-32
Table 16: System Level Testing Precision Results 6-33
Table 17: System Level Testing Accuracy Results 6-34
Table 18: Software Validation Testing 6-35
Table 19: Revision History 6-38
Table 20: Comparison to Reviewed Version 6-40
Table 21: AccuTnI Analytical Performance Section Summary 8-3
Table 22: Standardized Study LoB Results 8-6
Table 23: Multi-Temperature LoB Results 8-7
Table 24: Cross Temperature LoB Results 8-8
Table 25: Standardized Study LoD Results 8-10
Table 26: Multi-temperature LoD Precision Study Results 8-12
Table 27: Multi-temperature LoD Results 8-12
Table 28: Cross-temperature LoD Analysis, Between-Temperature SD 8-13
Table 29: Cross-temperature Analysis LoD Results 8-13
Table 30: Standardized Study LoQ Results 8-15
Table 31: LoQ Multi-temperature Summary 8-17
Table 32: LoQ Summary – Between-temperature Precision 8-17
Table 33: Cross-temperature LoQ Analysis based on the Multi-temperature Study 8-19
Table 34: Cross-temperature LoQ Analysis, Overall Multi-temperature Study Results 8-19
Table 35: Cross-temperature LoQ Analysis, Overall Standardized Study Results 8-19
Table 36: Total Precision Results, 18°C Temperature Set Point 8-23
Table 37: Total Precision, 28°C Temperature Set Point 8-23
Table 38: Total Precision, NLC (20°C to 24°C) 8-24
Table 39: Multi-temperature Study Precision Results 8-25
Table 40: Cross-temperature Precision Analysis Results 8-26
Table 41: Linearity Sample Concentrations 8-28
Table 42: Summary of Linearity Results at 18°C 8-29
Table 43: Summary of Linearity Results at 28°C 8-29
Table 44: Summary of Linearity Results at NLC 8-29
Table 45: Access AccuTnI High Dose Hook Effect Results 8-31
Table 46: Stability Testing Summary 8-33
Table 47: Reagent Pack Real Time Stability Results, Lot 116676 8-35
Table 48: Reagent Pack Real Time Stability Results, Lot 116677 8-36
Table 49: Reagent Pack Real Time Stability Results, Lot 116678 8-37
Table 50: Reagent Open Pack Stability Results, Concentration in ng/mL 8-39
Table 51: Reagent Open Pack Stability - Means Compared to Baseline Values 8-40
Table 52: Stored Calibration Curve Stability Results, Concentration in ng/mL 8-42
Table 53: Stored Calibration Curve Stability - Means Compared to Baseline 8-43
Table 54: Calibrator Real Time Stability Results, Lot 117302 8-46
Table 55: Calibrator Real Time Stability Results, Lot 117455 8-47
Table 56: Calibrator Real Time Stability Results, Lot 119776 8-48
Table 57: Calibrator Open Vial Stability Results, % Difference, Day 8 8-50
Table 58: Assay Validity Control Data for Day 8 Testing 8-50

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 59: Interfering Substances Results 8-53
Table 60: Dopamine Dilution Series 8-54
Table 61: Cross-Reactivity Results 8-56
Table 62: Lithium Heparin Plasma vs. Serum Comparison 8-57
Table 63: Thermal Sensitivity/Robustness Results 8-62
Table 64: Study Design for Concordance/Agreement Testing 8-62
Table 65: Thermal Sensitivity/Concordance Results, 0.02 ng/mL Cutoff 8-64
Table 66: Relative Low/High Temperature Concordance, 0.02 ng/mL Cutoff 8-64
Table 67: Thermal Sensitivity/Concordance Results, 0.03 ng/mL Cutoff 8-64
Table 68: Relative Low/High Temperature Concordance, 0.03 ng/mL Cutoff 8-64
Table 69: Method Comparison by Temperature 8-66
Table 70: Analytical Performance Summary 8-70
Table 71: Internal Study Thermal Program 10-2
Table 72: Internal Algorithm Field Effectiveness Study Results 10-4
Table 73: External Study Clinical Trial Precision Results–Reagent Lot 1 10-6
Table 74: External Study Clinical Trial Precision Results–Reagent Lot 2 10-7
Table 75: External Study Clinical Trial Precision Results–Reagent Lot 3 10-8

Figures

Figure 1: Application of the Thermal Algorithm 6-4
Figure 2: Access Immunoassay Family Instrument Hardware Platform 6-7
Figure 3: Instrument Case Temperature Circuit 7-2
Figure 4: LoQ Overall Limit of Quantitation, From Standardized Studies 8-20
Figure 5: Access AccuTnI Hook Effect 8-32
Figure 6: Reagent Open Pack Stability Linear Regression 8-40
Figure 7: Stored Calibration Curve Stability Linear Regression 8-43
Figure 8: Passing-Bablok Plot, 18°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL 8-57
Figure 9: Passing-Bablok Plot, 23°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL 8-58
Figure 10: Passing-Bablok Plot, 28°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL 8-58
Figure 11: Passing-Bablok Plot, 18°C vs. 23°C, Concentrations in ng/mL 8-66
Figure 12: Passing-Bablok Plot, 18°C vs. 28°C, Concentrations in ng/mL 8-67
Figure 13: Passing-Bablok Plot, 23°C vs. 28°C, Concentrations in ng/mL 8-67

Appendices

Appendix 1: Risk Management Scoring Criteria
Appendix 2: Access 2 3.3 Work Item Risk Assessment
Appendix 3: Access 2 3.3 System Software Change Risk Assessment
Appendix 4: Access 2 System Risk Assessment (SRA)
Appendix 5: Thermal Software Requirements
Appendix 6: Access 2 System Software Specification
Appendix 7: NexStep Configuration Requirements
Appendix 8: NexStep Diagnostics Requirements
Appendix 9: NexStep Data Reduction Requirements
Appendix 10: Thermal Algorithm Design Traceability Matrix
Appendix 11: Access 2 Software Design Description Document
Appendix 12: Access 2 3.3 Work Item Inclusion List
Appendix 13: Access 2 3.3 Unit Test Summary
Appendix 14: Access 2 3.3 Integration Test Summary
Appendix 15: Access 2 3.3 Software Testing and Software Validation Plan
Appendix 16: Access 2 3.3 Software Testing and Software Validation Summary
Appendix 17: Access 2 3.3 System Integration Software Testing Protocol
Appendix 18: Access 2 3.3 System Integration Software Testing Report

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Appendix 19: Access 2 3.3 IVD System Integration Software Testing Protocol
Appendix 20: Access 2 3.3 IVD System Integration Software Testing Report
Appendix 21: Access 2 3.3 Software System Level Test Protocol
Appendix 22: Access 2 3.3 Software System Level Test Report
Appendix 23: Access 2 3.3 Unresolved Anomalies
Appendix 24: TA056 Thermal Control Hardware Temperature Verification Plan
Appendix 25: TA060 Thermal Control Hardware Temperature Verification Report
Appendix 26: Standardized LoQ Precision Results and Profile Plots
Appendix 27: Multi-temperature LoQ Precision Results and Profile Plots
Appendix 28: Supplemental Linearity Results
Appendix 29: Thermal Concordance Results by Individual Sample
Appendix 30: Thermal Method Comparison Results, Mean Dose by Individual Sample
Appendix 31: Labeling

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Section 1.0

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1.0 Administrative

1.1. Medical Device User Fee Cover Sheet

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Form Approved. OMB No. 0910-511. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
MEDICAL DEVICE USER FEE COVER SHEET

PAYMENT IDENTIFICATION NUMBER: (b) (4) [redacted]
Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)

BECKMAN COULTER INC
1000 Lake Hazeltine Drive
Chaska MN 55318
US

1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)
*****0600

2. CONTACT NAME
Cindy McGuire

2.1 E-MAIL ADDRESS
cmcguire@beckman.com

2.2 TELEPHONE NUMBER (include Area code)
952-368-1142

2.3 FACSIMILE (FAX) NUMBER (include Area code)
952-368-7610

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/oc/mdufma

Select an application type:
[X] Premarket notification(510(k)); except for third party
[ ] 513(g) Request for Information
[ ] Biologics License Application (BLA)
[ ] Premarket Approval Application (PMA)
[ ] Modular PMA
[ ] Product Development Protocol (PDP)
[ ] Premarket Report (PMR)
[ ] Annual Fee for Periodic Reporting (APR)
[ ] 30-Day Notice

3.1 Select a center
[X] CDRH
[ ] CBER

3.2 Select one of the types below
[X] Original Application

Supplement Types:
[ ] Efficacy (BLA)
[ ] Panel Track (PMA, PMR, PDP)
[ ] Real-Time (PMA, PMR, PDP)
[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)
[ ] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
[X] NO, I am not a small business
4.1 If Yes, please enter your Small Business Decision Number:

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?
[X] YES (All of our establishments have registered and paid the fee, or this is our first device, and we will register and pay the fee within 30 days of FDA's approval/clearance of this device.)
[ ] NO (If "NO," FDA will not accept your submission until you have paid all fees due to FDA. This submission will not be processed; see http://www.fda.gov/cdrh/mdufma for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.
[ ] This application is the first PMA submitted by a qualified small business, including any affiliates
[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only
[ ] The sole purpose of the application is to support conditions of use for a pediatric population
[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).
[ ] YES [X] NO

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[Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION
(b) (4) [redacted]

14-Mar-2012

Form FDA 3601 (01/2007)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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1.2. CDRH Premarket Review Submission Cover Sheet

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 9010-0120
Expiration Date: December 31, 2013.
See OMB Statement on page 5.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number (if known)
April 20, 2012	MD 6060767-956733	

SECTION A TYPE OF SUBMISSION

PMA	PMA & HDE Supplement	PDP	510(k)	Meeting
☐ Original Submission	☐ Regular (180 day)	☐ Original PDP	☒ Original Submission:	☐ Pre-510(K) Meeting
☐ Premarket Report	☐ Special	☐ Notice of Completion	☒ Traditional	☐ Pre-IDE Meeting
☐ Modular Submission	☐ Panel Track (PMA Only)	☐ Amendment to PDP	☐ Special	☐ Pre-PMA Meeting
☐ Amendment	☐ 30-day Supplement		☐ Abbreviated (Complete section I, Page 5)	☐ Pre-PDP Meeting
☐ Report	☐ 30-day Notice		☐ Additional Information	☐ Day 100 Meeting
☐ Report Amendment	☐ 35-day Supplement		☐ Third Party	☐ Agreement Meeting
☐ Licensing Agreement	☐ Real-time Review			☐ Determination Meeting
	☐ Amendment to PMA &HDE Supplement			☐ Other (specify)
	☐ Other			

IDE	Humanitarian Device Exemption (HDE)	Class II Exemption Petition	Evaluation of Automatic Class III Designation (De Novo)	Other Submission
☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ 513(g)
☐ Amendment	☐ Amendment	☐ Additional Information	☐ Additional Information	☐ Other (describe submission):
☐ Supplement	☐ Supplement			
	☐ Report			
	☐ Report Amendment			

Have you used or cited Standards in your submission? ☐ Yes ☐ No (If Yes, please complete Section I, Page 5)

SECTION B SUBMITTER, APPLICANT OR SPONSOR

Company / Institution Name Beckman Coulter, Inc	Establishment Registration Number (if known) 2122870		
Division Name (if applicable)	Phone Number (including area code) (952) 368-1383		
Street Address 1000 Lake Hazeltine Drive	FAX Number (including area code) (952) 368-7610		
City Chaska	State / Province MN	ZIP/Postal Code 55318	Country USA
Contact Name Valynda Machen			
Contact Title Group Manager, Regulatory Affairs	Contact E-mail Address vmachen@beckman.com		

SECTION C APPLICATION CORRESPONDENT (e.g., consultant, if different from above)

Company / Institution Name			
Division Name (if applicable)	Phone Number (including area code) ( )		
Street Address	FAX Number (including area code) ( )		
City	State / Province	ZIP/Postal Code	Country
Contact Name			
Contact Title	Contact E-mail Address		

Questions or Contact FDA/CDRH/OCE/DIB at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION D1 REASON FOR APPLICATION - PMA, PDP, OR HDE

- ☐ Withdrawal
- ☐ Additional or Expanded Indications
- ☐ Request for Extension
- ☐ Post-approval Study Protocol
- ☐ Request for Applicant Hold
- ☐ Request for Removal of Applicant Hold
- ☐ Request to Remove or Add Manufacturing Site

- ☐ Change in design, component, or specification:
  - ☐ Software / Hardware
  - ☐ Color Additive
  - ☐ Material
  - ☐ Specifications
  - ☐ Other (specify below)

- ☐ Location change:
  - ☐ Manufacturer
  - ☐ Sterilizer
  - ☐ Packager

- ☐ Process change:
  - ☐ Manufacturing
  - ☐ Sterilization
  - ☐ Packaging
  - ☐ Other (specify below)

- ☐ Labeling change:
  - ☐ Indications
  - ☐ Instructions
  - ☐ Performance
  - ☐ Shelf Life
  - ☐ Trade Name
  - ☐ Other (specify below)

- ☐ Report Submission:
  - ☐ Annual or Periodic
  - ☐ Post-approval Study
  - ☐ Adverse Reaction
  - ☐ Device Defect
  - ☐ Amendment

- ☐ Response to FDA correspondence:

- ☐ Change in Ownership
- ☐ Change in Correspondent
- ☐ Change of Applicant Address

- ☐ Other Reason (specify):

SECTION D2 REASON FOR APPLICATION - IDE

- ☐ New Device
- ☐ New Indication
- ☐ Addition of Institution
- ☐ Expansion / Extension of Study
- ☐ IRB Certification
- ☐ Termination of Study
- ☐ Withdrawal of Application
- ☐ Unanticipated Adverse Effect
- ☐ Notification of Emergency Use
- ☐ Compassionate Use Request
- ☐ Treatment IDE
- ☐ Continued Access

- ☐ Change in:
  - ☐ Correspondent / Applicant
  - ☐ Design / Device
  - ☐ Informed Consent
  - ☐ Manufacturer
  - ☐ Manufacturing Process
  - ☐ Protocol - Feasibility
  - ☐ Protocol - Other
  - ☐ Sponsor

- ☐ Report submission:
  - ☐ Current Investigator
  - ☐ Annual Progress Report
  - ☐ Site Waiver Report
  - ☐ Final

- ☐ Repose to FDA Letter Concerning:
  - ☐ Conditional Approval
  - ☐ Deemed Approved
  - ☐ Deficient Final Report
  - ☐ Deficient Progress Report
  - ☐ Deficient Investigator Report
  - ☐ Disapproval
  - ☐ Request Extension of Time to Respond to FDA
  - ☐ Request Meeting
  - ☐ Request Hearing

- ☐ Other Reason (specify):

SECTION D3 REASON FOR SUBMISSION - 510(k)

- ☒ New Device
- ☐ Additional or Expanded Indications
- ☐ Change in Technology

☒ Other Reason (specify):
Software changes in Access 2 Immunoassay System

Questions or Contact FDA/CDRH/OSEIDI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	MMI	2	JIS	3	JJE	4	
5		6		7		8	

Summary of, or statement concerning, safety and effectiveness information
☒ 510 (k) summary attached
☐ 510 (k) statement

Information on devices to which substantial equivalence is claimed (if known)

	510(k) Number		Trade or Proprietary or Model Name		Manufacturer
1	K053020	1	TnI-Ultra™ Assay and Calibrators for the ADVIA Centaur® System	1	Siemens
2	K922823/A007	2	Access 2 Immunoassay System	2	Beckman Coulter, Inc
3		3		3	
4		4		4	
5		5		5	
6		6		6	

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification
Troponin I Enzyme Immunoassay; Discrete photometric chemistry analyzer for clinical use

	Trade or Proprietary or Model Name for This Device		Model Number
1	Access AccuTnI Reagent and Calibrator for use on the Access 2 Immunoassay Systems	1	A98143; A98144
2	Access 2 Immunoassay System	2	81600N
3		3	
4		4	
5		5	

FDA document numbers of all prior related submissions *(regardless of outcome)*

1	2	3	4	5	6
K093558	K021814	K010429	K922823/A007		
7	8	9	10	11	12

Data Included in Submission
☒ Laboratory Testing ☐ Animal Trials ☒ Human Trials

SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code	C.F.R. Section (if applicable)	Device Class
MMI, JJE	21CFR862.1215; 21CFR862.2160	☐ Class I ☒ Class II ☐ Class III ☐ Unclassified
Classification Panel Clinical Chemistry		

Indications (from labeling)

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.
Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.
The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.
Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.
The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Questions? Contact FDA/CDRH/OSEDID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Note: Submission of this information does not affect the need to submit a 2891 or 2891a Device Establishment Registration form.	FDA Document Number (if known)

SECTION H MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number 2122870	☒ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler		
Company / Institution Name Beckman Coulter, Inc		Establishment Registration Number 2122870		
Division Name (if applicable)		Phone Number (including area code) (952) 368-1383		
Street Address 1000 Lake Hazeltine Drive		FAX Number (including area code) (952) 368-7610		
City Chaska		State / Province MN	ZIP/Postal Code 55318	Country USA
Contact Name Valynda Machen	Contact Title Group Manager, Regulatory Affairs		Contact E-mail Address vmachen@beckman.com	

☐ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler		
Company / Institution Name		Establishment Registration Number		
Division Name (if applicable)		Phone Number (including area code) ( )		
Street Address		FAX Number (including area code) ( )		
City		State / Province	ZIP/Postal Code	Country
Contact Name	Contact Title		Contact E-mail Address	

☐ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager / Relabeler		
Company / Institution Name		Establishment Registration Number		
Division Name (if applicable)		Phone Number (including area code) ( )		
Street Address		FAX Number (including area code) ( )		
City		State / Province	ZIP/Postal Code	Country
Contact Name	Contact Title		Contact E-mail Address	

Questions? Contact FDA/CDRH/OCE/DIP at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION I UTILIZATION OF STANDARDS

Note: Complete this section if your application or submission cites standards or includes a "Declaration of Conformity to a Recognized Standard" statement.

	Standards No.	Standards Organization	Standards Title	Version	Date
1					
2					
3					
4					
5					
6					
7					

Please include any additional standards to be cited on a separate page.

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Rockville, MD 20850

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1.3. Required Elements Checklist

Section 510(k) element	Section
MDUFMA Cover Sheet	1.1
CDRH Premarket Review Submission Cover Sheet	1.2
510(k) Cover Letter	Page i
Indications for Use Statement	1.4
510(k) Summary or 510(k) Statement	1.6
Truthful and Accuracy Statement	1.5
Class III Summary and Certification	1.8
Financial Certification or Disclosure Statement	1.7
Declarations of Conformity and Summary Reports (Abbreviated 510(k)s)	N/A
Executive Summary	3.0
Device Description	4.0
Substantial Equivalence Discussion	5.0
Proposed Labeling	11.0
Sterilization/Shelf Life	N/A
Biocompatibility	N/A
Software	6.0
Electromagnetic Compatibility/Electrical Safety	N/A
Performance Testing – Bench	8.0
Performance Testing – Animal	N/A
Performance Testing – Clinical	9.0
Certification of Compliance with Requirements of ClinicalTrials.govData bank	9.19

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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1.4. Indications for Use Statement

The Indications for Use Form is provided on the following pages.

Questions? Contact FDA/CDRH/OSE/DIS at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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see reused

Indications for Use Form

510(k) Number (if known): _____

Device Name: Access AccuTnI Reagent and Calibrator for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

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The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use		Over-The-Counter Use
X	AND/OR	
(Part 21 CFR 801 Subpart D)		(21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

_____

Division Sign-Off

Office of In Vitro Diagnostic Device

Evaluation and Safety

510(k)_____

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1.5. Truthful and Accurate Statement

April 20, 2012

PREMARKET NOTIFICATION

TRUTHFUL AND ACCURATE STATEMENT

As Required by 21 CFR 807.87(k)

To the best of my knowledge, the data and information submitted in this premarket notification are truthful and accurate, and no material fact has been omitted.

Helmut Koehler
VP Global Research and Development

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See revised

1.6. 510(k) Summary

510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is _____

Submitted By:

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318
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Fax: (952) 368-7610

Contact Person:

Valynda Machen
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1383
Fax: (952) 368-7610

Date Prepared:

April 20, 2012

Device Name:

Proprietary / Trade Name: Access AccuTnI Reagent and Calibrator for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160

Predicate Devices:

The Access AccuTnI assay and calibrators claim substantial equivalence to

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the TnI-Ultra™ Assay and Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Device Description:

The Access AccuTnI reagents, AccuTnI calibrators and the Access 2 Instrument compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI Calibrator set contains multi-point calibrators for use with the Access AccuTnI assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

Intended Use:

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in

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human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI and the predicate device, ADVIA Centaur® TnI-Ultra™, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Similarities between the Access AccuTnI Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent	The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality,

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Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
	revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures. The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

Differences between the Access AccuTnI Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized : high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.01 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.78 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome

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Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.03 ng/mL	Total CV of ≤8% at concentrations >0.105 ng/mL. SD ≤0.0084 at concentrations ≤0.105 ng/mL

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Indication for Use	The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

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1.7. Financial Disclosure Statement

This information is provided in Section 9.0, Clinical Trial.

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1.8. Class III Product Summary and Certification

This is not a class III device, and is not substantially equivalent to a class III device; therefore the Literature Search and Certification requirement of the Safe Medical Devices Amendments (SMDA) of 1990 is not applicable.

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2.0 Intended Use / Indications for Use

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

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3.0 Executive Summary

3.1. Background

In March 2010, Beckman Coulter submitted a pre-IDE (I100255) to the Agency specifically to address changes that had been made to the AccuTnI device over time. During the review of the pre-IDE, the Agency provided Beckman Coulter with a "Points to Consider" document to ensure that the performance of the AccuTnI device would meet the current clinical needs reflected in the Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines and the Joint ESC/ACCF/AHA/WHF Task Force Guidelines that pertain to diagnosis of myocardial infarction (collectively "MI Guidelines").[1] Also, through the course of the pre-IDE discussions, Beckman Coulter obtained extensive FDA feedback on the proposed clinical trial and analytical study designs. This feedback was incorporated into both the analytical study plans and the clinical trial protocols.

Subsequently, Beckman Coulter discovered that changes in instrument operating temperatures could affect the accuracy of AccuTnI measurement. To address this thermal sensitivity, Beckman Coulter took two steps. First, in April 2011 Beckman Coulter issued a recall notice (PCA 16241) to inform customers of the issue and to restrict the temperature range the device could be used at in order to minimize the impact of temperature on performance. Second, Beckman Coulter designed a comprehensive solution to minimize the effects of thermal sensitivity and provide a larger, less restrictive temperature range to customers. This solution is a software algorithm that normalizes troponin results based on internal instrument temperatures (which are

[1] *Available at* http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm230118.htm.

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measured using a thermistor found in currently fielded instruments) during a sample run and during the associated calibration run. This solution is implemented through a combination of system and operating software changes.

In order to demonstrate the effectiveness of the thermal solution, Beckman Coulter redesigned the previously agreed upon analytical studies to incorporate extensive variable temperature testing after having several discussions with FDA and addressing the feedback it received (I100255/S002).

The results of these studies provided data for the AccuTnI assay on the Access 2 Immunoassay System that, among other things, demonstrated:

- High clinical sensitivity and specificity when evaluated in a multi-center pivotal clinical trial of 1,929 subjects, and
- All pre-defined acceptance criteria were met for analytical testing studies conducted across the operating range of 18°C to 28 °C.

Further details are provided below and throughout this document.

3.2. Device Description

Access AccuTnI consists of reagent packs, calibrators and the AccuTnI Assay Protocol File (APF) which contains all the parameters used to process the AccuTnI assay. Access AccuTnI, together with the Access 2 Immunoassay System (instrument) provide for the quantitative determination of cTnI levels in human serum and plasma using paramagnetic particle solid phase technology and chemiluminescent signal detection. Calibrators, quality controls, and patient samples containing cTnI are analyzed in a two-site immunoenzymatic ("sandwich") assay. A detailed device description for the AccuTnI assay, calibrators, and Access 2 instrument is located in Section 4.0, Device Description.

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3.3. Substantial Equivalence

Beckman Coulter believes the Access 2 AccuTnI assay is substantially equivalent to the ADVIA Centaur® TnI-Ultra™, K053020, and the Access 2 Immunoassay System is substantially equivalent to the Access 2 Immunoassay System, K922823/A007. Information on similarities and differences can be found in Section 5.0, Substantial Equivalence Discussion.

3.4. Performance Testing

Testing for the AccuTnI assay on the Access Immunoassay Systems included:

- Extensive software development, testing, and validation;
- Comprehensive analytical testing that included extensive testing at multiple temperatures to establish the analytical performance of the AccuTnI assay on the Access 2 Immunoassay System; and
- A pivotal clinical trial with nearly 2000 subjects, which, together with other data and information, supports substantial equivalence to the predicate device and demonstrates the ability of the system to meet current medical needs described in the MI Guidelines.

Summaries of these activities are provided below.

Software Verification and Validation

Extensive software verification and validation testing ensured that the Access 2 system software version 3.3 design outputs met the requirements of the design inputs and conformed to the user needs and intended use. The objectives of the testing were to:

- Verify the design changes to the system software
- Verify the thermal software requirements
- Verify that no unintended changes have been introduced
- Verify the correct installation of system software for the Access 2

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- Validate that the operation of the system software conforms to user needs and intended use

A detailed discussion of software changes and the associated verification and validation activities are provided in Section 6.0, System Software.

Analytical Performance

Analytical performance testing was performed in support of the development of this product and a summary of this testing and the results is provided in Attachment 1 of the Executive Summary section. Detailed descriptions of these studies are provided in see Section 8.0, Analytical Performance.

Clinical Trials

The clinical efficacy of Access AccuTnI was demonstrated by two clinical trials. In the first study, a prospective feasibility trial was conducted to determine study sample size and propose a clinical cut-off to be validated in a prospective pivotal trial. In the second study, a prospective trial of apparently healthy individuals was conducted to establish and characterize an upper reference limit.

The prospective multi-center Pivotal Trial was designed and conducted based on the prospective Feasibility Trial, the FDA document "Points to Consider for Troponin pre-IDE and 510(k) Submissions" (April 30, 2010), the pre-IDE discussions with FDA, and the scientific literature and cardiology guidelines. A total of 1,929 patients presenting with symptoms suspicious for acute myocardial infarction with serial plasma samples were evaluated in this Pivotal Trial. Diagnoses used as "truth" in the study were adjudicated by a trained expert central panel that was blinded to results from Access AccuTnI testing. Significant diagnostic efficacy was demonstrated in both the

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Feasibility Trial and the Pivotal Trial at all time intervals after Emergency Department admission and at all time intervals after symptom onset.

The Feasibility Trial ROC curve analysis determined that a cutoff of 0.03 ng/mL yielded 95% sensitivity. This proposed cutoff was validated by the larger multi-center Pivotal Trial where a cutoff of 0.03 ng/mL yielded 94.3% (91 to 98%) sensitivity. This 0.03 ng/mL cutoff is within the 95% CI of results from the Feasibility Trial.

Details of this study are provided in Section 9.0, Clinical Trial.

3.5. Conclusion

The information provided in the sections cited above demonstrates that the proposed new device, the Access AccuTnI assay, has the same intended use as the predicate device. Moreover, the Access 2 instrument, which was modified to address thermal sensitivity, has the same intended use as the predicate device. In addition, verification and validation testing, the clinical and analytical data, the clinical use of the product reflected in current MI diagnostic guidelines, and other scientific information provided in this submission demonstrate that the Access AccuTnI assay on the Access 2 Immunoassay Systems is as safe and effective as the predicate devices. Taken together, this information establishes the substantial equivalence of Beckman Coulter's products to predicates.

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Attachment 1: Analytical Performance Summary

Study	510(k) Section	Study Description	Acceptance Criteria	Results	Pass/Fail
Limit of Blank	**8.1**	18°C EP17-A	LoB ≤0.010 ng/mL	0.004 ng/mL	Pass
		NLC EP17-A		0.003 ng/mL	Pass
		28°C EP17-A		0.004 ng/mL	Pass
		Multi-Temp		0.003 ng/mL	Pass
		Cross-Temp Analysis	LoB within 0.010 ng/mL of each temp	0.001 ng/mL	Pass
Limit of Detection	**8.2**	18°C EP17-A	LoD ≤0.030 ng/mL	0.006 ng/mL	Pass
		NLC EP17-A		0.005 ng/mL	Pass
		28°C EP17-A		0.009 ng/mL	Pass
		Multi-Temp	SD ≤0.0084 ng/mL LoD ≤0.030 ng/mL	Max SD = 0.0038 ng/mL LoD = 0.009 ng/mL	Pass
		Cross-Temp Analysis	SD ≤0.0084 ng/mL LoD ≤0.030 ng/mL	Max SD = 0.0052 ng/mL LoD = 0.010 ng/mL	Pass
Limit of Quantitation	**8.3**	18°C EP17-A	10% LoQ ≤0.06 ng/mL 20% LoQ ≤0.03 ng/mL	Max 10% LoQ = 0.02 ng/mL Max 20% LoQ = 0.01 ng/mL	Pass
		NLC EP17-A		Max 10% LoQ = 0.03 ng/mL Max 20% LoQ = 0.01 ng/mL	Pass
		28°C EP17-A		Max 10% LoQ = 0.04 ng/mL Max 20% LoQ = 0.02 ng/mL	Pass
		Multi-Temp	10% LoQ ≤0.06 ng/mL 20% LoQ ≤0.03 ng/mL SD ≤0.0084 ng/mL or CV ≤8%	Max 10% LoQ = 0.03 ng/mL Max 20% LoQ = <0.01 ng/mL Max SD = 0.0047 ng/mL Max CV = 3%	Pass
		Cross-Temp Analysis	10% LoQ ≤0.06 ng/mL 20% LoQ ≤0.03 ng/mL SD ≤0.0084 ng/mL or CV	Max 10% LoQ = 0.04 ng/mL Max 20% LoQ = 0.02 ng/mL Max SD = 0.0055 ng/mL	Pass

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Attachment 1: Analytical Performance Summary

Study	510(k) Section	Study Description	Acceptance Criteria	Results	Pass/Fail
			≤8%	Max CV = 4%	
Precision	**8.4**	18°C EP5-A2	SD ≤0.0084 ng/mL or CV ≤8%	Max SD = 0.0030 ng/mL Max CV = 5%	Pass
		NLC EP5-A2		Max SD = 0.0032 ng/mL Max CV = 3%	Pass
		28°C EP5-A2		Max SD = 0.0050 ng/mL Max CV = 6%	Pass
		Multi-Temp		Max SD = 0.0020 ng/mL Max CV = 6%	Pass
		Cross-Temp Analysis		Max SD = 0.0030 ng/mL Max CV = 8%	Pass
Linearity	**8.5**	18°C EP6-A	p >0.05 or bias ≤16%	Max bias = 10%	Pass
		NLC EP6-A		Max bias = 9%	Pass
		28°C EP6-A		Max bias = 8%	Pass
High Dose Hook Effect	**8.6**	NLC	No hook effect from S5 calibrator concentration up to at least 2,000 ng/mL.	No hook at 2,529 ng/mL	Pass
Reagent pack real time stability	**8.7**	NLC	Target = 12 months	Stable for 6 months; study ongoing	Pass
Reagent open pack stability			Stable for ≥35 days	Stable for 56 days	Pass
Stored calibration curve stability			Stable for ≥35 days	Stable for 56 days	Pass
Calibrator real time stability			Target = 12 months	Stable for 4 months; study ongoing	Pass
Calibrator open vial stability			Target = 60 days	Stable for 8 days; study ongoing	Pass
Interference and Analytical Specificity	**8.8**	18°C EP7-A2	Interference ≤10.0%	No interference >10.0%	Pass
		NLC EP7-A2			Pass
		28°C EP7-A2			Pass

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Attachment 1: Analytical Performance Summary

Study	510(k) Section	Study Description	Acceptance Criteria	Results	Pass/Fail
Cross-reactivity	**8.9**	18°C EP7-A2	Cross-reactivity ≤1.00%	Max cross-reactivity = 0.11%	Pass
		NLC EP7-A2		Max cross-reactivity = 0.08%	Pass
		28°C EP7-A2		Max cross-reactivity = 0.06%	Pass
Sample Matrix Comparison	**8.10**	18°C	Slope = 1.00 ±0.10 r >0.95	Slope = 1.03, r = 0.99	Pass
		23°C		Slope = 1.02, r = 0.99	Pass
		28°C		Slope = 1.04, r = 0.99	Pass
HAMA / Heterophile	**8.11**	NLC	Characterize blocker effectiveness	The AccuTnI reagent pack has been formulated to minimize the effects of HAMA and Heterophile interference.	Pass
Thermal Sensitivity – Robustness	**8.12**	Six Temperatures	p >0.05 or slope ≤0.010	Max slope = -0.007	Pass
Thermal Sensitivity – Impact on Low Dose Concordance / Agreement	**8.13**	Six Temperatures	p >0.05 or concordance ≥90% Bias ≤0.0084 ng/mL	0.02 ng/mL analysis: Concordance 93%, Bias = 0.0065 ng/mL 0.03 ng/mL analysis: Concordance 91%, Bias = 0.0082 ng/mL	Pass
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison	**8.14**	18°C vs 23°C	Slope = 1.00 ±0.10 r >0.95	Slope = 1.01, r = 1.00	Pass
		18°C vs 28°C		Slope = 0.98, r = 1.00	Pass
		23°C vs 28°C		Slope = 0.97, r = 1.00	Pass

Note: Normal laboratory conditions (NLC) is the actual recorded temperature(s) that occurred in the laboratory on the day(s) of the study.

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4.0 Device Description

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Access AccuTnI consists of reagent packs, calibrators and the AccuTnI Assay Protocol File (APF) which contains all the parameters used to process the AccuTnI assay. Access AccuTnI together with the Access 2 Immunoassay

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System provide for the quantitative determination of cTnI levels in human serum and plasma using paramagnetic particle solid phase technology and chemiluminescent signal detection. Calibrators, quality controls, and samples containing cTnI are analyzed in a two-site immunoenzymatic ("sandwich") assay, using alkaline phosphatase conjugated mouse monoclonal anti-human cTnI and paramagnetic particles coated with mouse monoclonal anti-human cTnI. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody-alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

The following paragraphs describe the Access AccuTnI Reagent and Calibrator Kits, the general purpose substrate and wash buffer, and an overview of the Access 2 Immunoassay Instrument.

4.1. Reagent Kit

The Access AccuTnI Reagent Kit consists of two reagent packs. Each reagent pack contains four reagents:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.

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- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

4.2. Calibrator Kit

The Access AccuTnI Calibrator Kit consists of ready-to-use, liquid, multi-point calibrators for use with Access AccuTnI Reagent Kit. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. No changes have been implemented in the AccuTnI calibrator material as part of this submission; the antigen, the matrix, and the concentration of antigen at each level are identical to the previously cleared (K010429) Access AccuTnI Calibrators.

4.3. Substrate

The Access Substrate is a general purpose reagent that is an accessory used for all immunoassays on the Access 2. It is a dioxetane-based chemiluminescent compound. This chemiluminescent substrate, Lumi-Phos® 530, is added to the reaction vessel and light generated by the reaction is measured with a luminometer.

4.4. Wash Buffer

The Access Wash Buffer II is a general purpose reagent that is an accessory used for all immunoassays on the Access 2. It is TRIS-buffered saline containing surfactant and preservatives. It is used to clean the pipetting probe tip and wash paramagnetic particles to remove unbound analyte and excess reagents in each reaction.

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4.5. Access 2 Immunoassay System

The Access 2 Immunoassay System was cleared for marketing in the US under K922823/A007 (July 2, 2001). The following changes to address thermal sensitivity, described in software section 6.0, have been made to the Access 2 instrument and are included in this submission.

- Labeling of the ambient operating temperature range was changed to 18°C to 28°C
- Labeling of the instrument case temperature range (internal instrument temperature) of 18°C to 36°C was added.
- The requirement to accurately measure the instrument case temperature within ±1.0°C was implemented.
- Upgrades in system software version 3.3 were made which included the following:
    - Capability to recognize and apply algorithms provided in the APF
    - Result suppression when instrument case temperature (internal instrument temperature) is less than 18°C or greater than 36°C
    - Implementation of the "U" Command to improve mixing of the paramagnetic particle reagent

The Access 2 is a member of the Access Immunoassay System instrument family, which is comprised of microcomputer controlled, random-access and continuous-access instruments. The instruments perform enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction.

The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to

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the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into the system. The APF contains all assay-specific parameters used to process a particular assay, including:

- Identification of reagents used to process the assay
- The sequence and volumes of the sample and reagent additions
- Mixing parameters
- Incubation times
- Math model used to convert the measured response to a reportable result
- Calibration information
- Thermal algorithm

Both the Access 2 instrument technology and its chemiluminescent assay format are well established and do not introduce any new risks associated with new technologies or methods of analysis. There are currently over 50 assays cleared or approved for use on the Access 2 instrument developed by Beckman Coulter that utilize the same technology as Access AccuTnI.

The major Access 2 system components which execute all system processing, control and interface functions are listed below and no changes to address thermal sensitivity have been made to them for this submission.

- Carousel Module
- Pipettor Module
- Analytical Module
- Fluidic Module
- Electronic/Systems Computer
- Peripheral Module

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5.0 Substantial Equivalence Discussion

Beckman Coulter believes the Access 2 AccuTnI assay is substantially equivalent to the ADVIA Centaur® TnI-Ultra™, K053020 and the Access 2 Immunoassay System is substantially equivalent to the Access 2 Immunoassay System, K922823/A007.

Table 1 and Table 2 provide a summary of the pertinent similarities and differences between the Access AccuTnI reagents and calibrators and the predicate. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Table 1: Similarities between the Access AccuTnI Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack Configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk	The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

	stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures. The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction. Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The intended use, assay principle, test system, sample type, reagent pack configuration and primary reagent materials of the subject device are equivalent to those of the predicate device.

Table 2: Differences between the Access AccuTnI Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
Sample Type	EDTA Plasma	No EDTA Plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA

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Table 2: Differences between the Access AccuTnI Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI
Calibrators: number and type	Two Lyophilized : high and low (use with master curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (no master curve)
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.01 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.78 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02-0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01-0.05 ng/mL
Precision	Total CV of 10% at a level of 0.03 ng/mL	Total CV of ≤8% at concentrations >0.105 ng/mL. SD ≤0.0084 at concentrations ≤0.105 ng/mL

Table 3 and Table 4 provide a summary of the pertinent similarities and differences between the Access 2 Immunoassay System and the predicate.

Table 3: Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Indication for Use	The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	chemiluminescent	same

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Table 4: Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal Algorithm Capability	Not present	Present
APF	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18°C to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

As noted above, there are certain differences between the predicate device and the proposed new device; however, the devices have a common intended use and the differences do not raise new questions about safety and effectiveness. The proposed new device is as safe and effective as the predicate device as demonstrated by verification and validation testing, the clinical and analytical data, the clinical use of product reflected in current published MI diagnostic guidelines and other scientific information provided in this submission.

Therefore, Beckman Coulter believes the information provided in this submission demonstrates that the proposed new device is substantially equivalent to the predicate device.

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Section 6.0

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6.0 System Software

6.1. Level of Concern

The level of concern classification for the system software used on the Access 2 was determined to be Major for AccuTnI. Table 5 was generated by performing pre-mitigation assessment of the system using the "Determining Level of Concern" section in FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

Table 5: Level of Concern

1	Does the Software Device qualify as Blood Establishment Software?	No
2	Is the Software Device intended to be used in combination with a drug or biologic?	No
3	Is the Software Device an accessory to a medical device that has a Major Level of Concern?	No
4	Prior to mitigation of hazards, could a failure of the Software Device result in death or serious injury, either to a patient or to a user of the device? Examples include the following: a. Does the Software Device control a life supporting or life sustaining function?	No
	b. Does the Software Device control the delivery of potentially harmful energy that could result in death or serious injury, such as radiation treatment systems, defibrillators, and ablation generators?	No
	c. Does the Software Device control the delivery of treatment or therapy such that an error or malfunction could result in death or serious injury?	No
	d. Does the Software Device provide diagnostic information that directly drives a decision regarding treatment or therapy, such that if misapplied it could result in serious injury or death?	Yes
	e. Does the Software Device provide vital signs monitoring and alarms for potentially life threatening situations in which medical intervention is necessary?	No

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6.2. Software Description

6.2.1. Introduction

This section describes the Access 2 system software intended for use with Access AccuTnI and other Access assays. The system software documentation in this submission reflects the new system software version 3.3. The Access 2 system software documentation for software version 2.4 was previously reviewed and approved by FDA in P980041/S008. The changes made to the software from version 2.4 to 3.3 are listed in Section 6.10 Software Revision History.

The Access 2 has both instrument software and console PC software which are controlled by the new system software version 3.3. The Access 2 system software version 3.3 supports all instrument configurations since Access 2 instrument release.

As described in Sections 6.2.2 and 6.2.3, there are three changes in Access 2 system software version 3.3 to address thermal sensitivity. These changes consist of:

- the capability to apply a thermal algorithm, when present in an APF, to adjust the dose result from thermally sensitive assays. A thermal algorithm is being added to the AccuTnI APF.
- the capability to suppress the assay result for all assays when the instrument case temperature (internal instrument temperature) is less than 18°C or greater than 36°C.
- the capability to execute a "U" Command when present in an APF. The "U" Command applies to particle mixing in the reagent pack and is being added to the AccuTnI APF.

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(b) (4)

[redacted]

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(b) (4)

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(b) (4)

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Table 6: Device Features Controlled by Software

Feature	Change
Facilitating Operator Input through User Interface	None
Facilitating Direct Operator Interaction with Instrument	None
Scheduling Assays	None
Running Assays	The capability to execute the "U" Command when present in an assay specific APF has been added to the Access 2 system software version 3.3.
Calculating Results	The capability to execute assay specific thermal algorithms loaded from an APF has been added to the Access 2 system software version 3.3. The system software has also been modified to include assay result suppression when the instrument case temperature is less than 18°C or greater than 36 °C.
Monitoring/Controlling Instrument Environment	The Access 2 system software version 3.3 actively measures and monitors the instrument case temperature during a run with an existing internal instrument temperature sensor.
Storing Data in Database Files	The Access 2 system software version 3.3 records the case temperature during a run at 36 second intervals. The system software uses the recorded case temperatures to determine the temperature of an individual assay result and the temperature associated with the corresponding assay calibration.
Performing Maintenance and Diagnostic Routines	None
Facilitating Laboratory Information System (LIS) Communication	None
Printing Reports	None
Data-Driven Assay Processing	The capability to load assay specific thermal algorithms from an APF has been added to the Access 2 system software version 3.3.

6.2.5. Operational Environment

This section provides a description of the operational environment.

6.2.5.1. Hardware Platform

A diagram of the system hardware platform is shown below in Figure 2.

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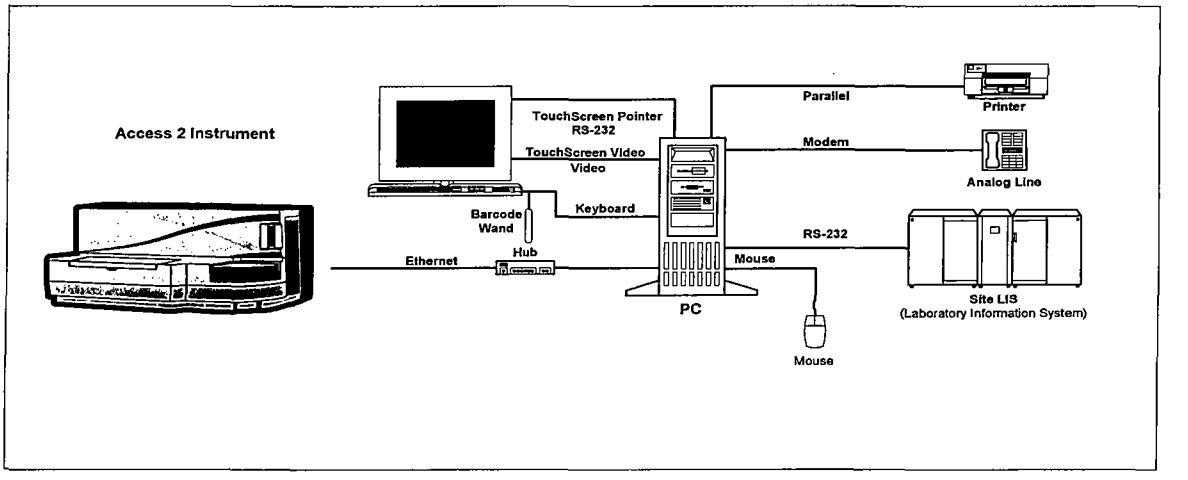

Figure 2: Access Immunoassay Family Instrument Hardware Platform

6.2.5.2. Programming Languages and Operating System

The PC operating system is either Windows NT (for instruments manufactured prior to March 2010) or Windows XP Embedded (XPe) (for instruments manufactured starting in March 2010 or instruments that have undergone a field upgrade); the PC portion of the system software is programmed in C++. The Access 2 instrument operating system is OS-9/X86 and the instrument system software portion is programmed in C. The off-the-shelf components are shown in Table 7.

Table 7: Off-the-Shelf Components

Category	PC	Access 2
Operating System	Windows NT or Windows XPe	OS-9/X86
Database	Poet	None
Basic Graphical User Interface Components	Microsoft Foundation Classes	None
Graphs (Cal, QC)	Chart FX	None
Report Generators	Crystal Reports by Seagate	None

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Table 7: Off-the-Shelf Components

Category	PC	Access 2
Utility Library	Microsoft Foundation Classes	None
Remote Diagnostics	PC Anywhere	None
Compiler	Visual C++	Hawk from Microware
Device Drivers	Drivers from I/O board vendors	Microware Drivers

6.3. Risk Management

Risk Management activities were performed for the Access 2 System Software 3.3 in accordance with Beckman Coulter procedures BCCP0082 (Product Safety Risk Management) and BCCP0083 (Risk Acceptability). These procedures are based on ISO 14971(2009). The purpose of the risk management activities was to identify hazards associated with the system software modification including use errors and foreseeable intentional misuse scenarios, to estimate and evaluate the risks, to control these risks, and to verify the effectiveness of these controls. Tables listing criteria for severity, probability of occurrence, probability of harm and risk acceptability are provided in Appendix 1. The risk management activities performed for the Access 2 system software version 3.3 are described in the paragraphs below.

6.3.1. Risk Management Plan

The Risk Management Plan describes the risk management activities to support the commercial release of Access 2 3.3 Software and also describes how the risks associated with the Access 2 3.3 Software will be monitored and managed following commercial release. The plan covers risk management activity responsibilities, risk acceptability criteria, risk assessment activities, verification of risk mitigation and controls, risk management reviews, and the post-launch risk management plan.

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6.3.2. Work Item Evaluation and Risk Assessment

A preliminary evaluation of the work items in the Access 2 3.3 Work Item Inclusion List was performed during the code review portion of the work item to identify high risk work items and assign a Concern Code of A through E. Table 8 contains the codes used to grade the work items.

Table 8: Concern Code Categories

Code	Risk Category	Description
A	High	New feature, major rework of critical module, change of hardware requiring new software, affects assay processing or APF Change. Critical module involved in the Work Item.
B	Moderate	This code is not used but retained in this table due to the tracking tool implementation.
C	Low	This change affects support functions.
D	Minor	This change affects minor support functions or implements minor code changes that will not impact the System Software.
E	None	Inconsequential changes such as: cosmetic change. No code change, no concern.

The Access 2 3.3 Work Item Risk Assessment, provided in Appendix 2, contains the risk assessment for individual work items with Concern Code A associated with the thermal adjustment of test results. Concern Code B is not used (See Table 8). Risk assessments for work items which have a Concern Code of C, D or E are outside the scope of the Risk Management Plan and were performed and documented within the work item itself in the Teams Foundation Server (TFS) tool.

The results of the risk assessment concluded:

- The work item test cases were adequate to verify that the changes were implemented as intended.
- Functionality was sufficiently covered by the test cases listed in the work item.

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- Design and code reviews determined that any risk identified was effectively mitigated and there was no identified resulting risk.

6.3.3. Access 2 3.3 System Software Change Risk Assessment

The Access 2 3.3 System Software Change Risk Assessment, provided in Appendix 3, documents the risk evaluation of implementing the changes listed in the Access 2 3.3 Work Item Inclusion List. The safety Failure Modes and Effect Analysis (FMEA) table grouped work items by functionality areas of change and evaluated the risk of each combined change group. Verification and validation activities were identified for each of these changes or set of changes. The verification and validation degree of rigor was commensurate with the risk level of the change.

Because the intent of the risk analysis was to encompass all assays available on the Access 2 platform, a worst-case severity was assumed. Thus, a severity of Life-threatening Injury was used in cases where a wrong result was identified as a hazardous situation. For instances where a delay in a result was identified as the hazardous situation a severity of Permanent Injury was used.

Post-Mitigation probability of occurrence and probability of harm scoring was assessed before performing the actual prescribed testing for the following reasons:

- First, these tests were not complete unless they all met acceptance criteria (ie: software changes were iterated until the prescribed test was successful). The post mitigation scoring reflected a passing test.
- Second, Post-Mitigation risk assessment was needed in order to evaluate the necessity for additional design mitigation, additional testing, or risk management activities.

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This approach allowed for proactive mitigation of any unacceptable risk. If necessary, an iterative risk assessment process was used until all risks were acceptable.

Each group of work items was verified to ensure the design met the intent of the change. Additional testing was prescribed if needed to increase the confidence level and to ensure completeness of design mitigation. The tests were not complete unless they passed; software changes were iterated until the prescribed test was successful.

6.3.4. Access 2 System Risk Assessment

The purpose of the Access 2 System Risk Assessment (SRA), provided in Appendix 4, is to summarize potential failure modes related to safety and corresponding hazardous situations, potential harms, mitigations/risk control measures, and the resulting residual risk profile and its acceptability for the Access 2 3.3 software design change for thermal mitigation. Existing FMEAs are the source documents for this SRA. The scope of the analysis applies to the Access 2 instrument and its system interface with operators and the environment.

All individual residual risks were in either Risk Zone I (Acceptable) or Risk Zone II (As Low as Reasonable Practicable (ALARP)). For risks that were in Risk Zone II, risk control measures to maintain risks in the ALARP zone represent the generally accepted state of the art. All appropriate testing was performed and controls were put in place to ensure that risks were as low as reasonably practicable.

6.3.5. Risk Management Review

Upon completion of risk management activities, a comprehensive risk management review was held to:

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- evaluate identified risks and their respective controls,
- ensure that residual risks are acceptable,
- anticipated failure modes are communicated to product support personnel,
- ensure methods are in place to obtain, review and trend post launch risk information, and
- ensure the risk management plan was appropriately implemented.

6.3.6. Risk Management Report and Conclusion

The overall residual risk profile was deemed acceptable. Post-mitigation, all identified risks were in either Risk Zone 1 (Acceptable) or Risk Zone II (ALARP). No risks were in Risk Zone III (Unacceptable). Based on objective evidence provided by feasibility, characterization, verification, and validation studies, all risks in the ALARP zone were determined to be as low as reasonably practicable. No new failure modes were identified and no new or increased risks were identified for existing failure modes.

In conclusion, for risks in Risk Zone 2 (ALARP), risk control measures to maintain risks in the ALARP zone represent the generally accepted state of the art where all performance characteristics related to safety meet (medical) requirements for the intended uses of the system software and are comparable to other systems in commercial distribution. All appropriate testing has been performed and controls put in place to ensure that risks are as low as reasonably practicable.

6.4. Software Requirements Specification

Software Requirements Specification (SRS) documents contain sections pertaining to the thermal algorithm and temperature monitoring. They are provided in the appendices indicated.

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Table 9: Software Requirements Specifications

Requirements Specification Document	Appendix
Thermal Software Requirements	Appendix 5
Access 2 System Software Specification	Appendix 6
NexStep* Configuration Requirements	Appendix 7
NexStep* Diagnostics Requirements	Appendix 8
NexStep* Data Reduction Requirements	Appendix 9

* NexStep is the Beckman Coulter development project name for the Access 2 instrument.

The specific requirements pertaining to the thermal algorithm and temperature monitoring or those that may be affected by these changes are traced in the Thermal Algorithm Design Traceability Matrix, provided in Appendix 10. Work items and test cases were developed to verify and validate the implementation of each of these requirements and are also listed in the Thermal Control Algorithm Design Traceability Matrix.

6.5. Architecture Design

No changes have been made to the architecture design for this submission.

6.6. Software Design Specification

The Access 2 Software Design Description Document, provided in Appendix 11, lists all of the documents that constitute the design or a description of the design of the Access 2 software. The intent is to list the critical items that if changed represent a possible change to the design. If any item listed in the Design Description Document were to change, an analysis would be performed to determine if the design had changed. Changing any listed item requires documentation describing the change and justification of actions taken.

6.7. Traceability

A design traceability matrix was created to map user needs, design inputs, requirements and verification and validation activities for the new thermal algorithm feature. The Thermal Algorithm Design Traceability Matrix is

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provided in Appendix 10. The software requirements were identified and tagged with unique requirement numbers. The test cases for verification and validation were likewise identified and tagged with unique test case numbers. Test cases were mapped in "many-to-one" or "one-to-many" relationships to the requirements.

Also, the Access 2 3.3 System Risk Assessment traces risks identified in the Access 2 3.3 System Software Change Risk Assessment to the requirements documents and to the Access 2 3.3 Software Testing and Software Validation Summary. The Access 2 3.3 Software Testing and Software Validation Summary traces the test cases for mitigation testing back to the work items in the Access 2 3.3 System Software Change Risk Assessment.

6.8. Software Development Process

Software development planning documents were prepared for the thermal algorithm project in accordance with Beckman Coulter Corporate Procedure BCCP0085, Software Development. This procedure is designed to be compliant with 21 CFR 820.30 and incorporates the software life cycle principles outlined in the CDRH guidance document, *General Principles of Software Validation.* Key activities in the process include planning, requirements development and verification, design, design verification, coding, code verification, software testing and validation, change control, configuration management, risk management, traceability, and design transfer. All required records necessary to demonstrate that the software was developed in accordance with the requirements of the procedure are maintained in a Design History File. The specific plans are listed in Table 10 and described below. Additionally, the Beckman Coulter Immunoassay Software team has adopted the Team Software Process (TSP) to help ensure delivery of safe and effective medical device software. The TSP is a software process framework developed by the Software Engineering Institute of Carnegie Mellon

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University. The TSP provides engineering teams with a disciplined set of planning, reviewing, and measuring practices designed to produce high reliability software. All plans are reviewed and approved by a cross-functional project management team, which includes quality assurance representation.

Table 10: Development Plans

Document
Thermal Control Algorithm Design and Development Plan
Thermal System Software Design and Development Plan
Access 2 Software Development Plan
Software Configuration Management Plan
Access 2 3.3 Software Risk Management Plan
Access 2 3.3 Software Testing and Software Validation Plan

6.8.1. Thermal Control Algorithm Design and Development Plan

This plan established the framework to manage the development and implementation of the thermal algorithm project. It includes a description of:

- the Troponin/Thermal Core Team that managed the program,
- approval authority for program deliverables,
- critical program coordination requirements,
- action tracking,
- high level product development process,
- mandatory design reviews, and
- Design History File and Project History File locations.

6.8.2. Thermal System Software Design and Development Plan

This plan established the framework to manage the thermal system software project and includes a description of:

- the System Software Element Team that managed the project,
- project phases,

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- action tracking,
- project communication and team interface,
- project deliverables responsibilities and approval authority,
- mandatory design reviews,
- technical and data reviews,
- design change management, and
- labeling changes.

6.8.3. Access 2 Software Development Plan

This document was used by the Software Development Team and Software Test Team members to assist in planning and executing tasks associated with the Access 2 3.3 software project. This plan included a description of:

- software requirements sources,
- software requirements verification,
- design and coding verification,
- work item unit test and work item integration test
- software verification and validation testing,
- independent review of testing,
- change control and configuration management (Microsoft Team Foundation Server (TFS), is used to document and to control changes to the software)
- supporting activities (risk management, use-error management, Off-The-Shelf software component management, software traceability, software inspection summary),
- software documentation including Design History File and Design Transfer,
- resources, schedule, and project deliverables,
- work item process for tracking defects found during testing, and

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- review types including formal team review, peer desk review and team walk-through review.

6.8.4. Software Configuration Management Plan

This plan is used by the software developers and describes how software configuration is managed and controlled. It ensures the following:

- source code is controlled using the Microsoft Team Foundation Server tools in conjunction with policies and procedures,
- all elements (Configuration Items: files and directories) that are inputs for the build process are version controlled,
- Change Point Analysis is performed on every verification build entering the formal verification phase
    - to analyze software changes implemented during formal software verification
    - to determine which software functions and test procedures have been impacted and need re-verification,
- any changes to configuration require revalidation.

6.8.5. Access 2 3.3 Software Risk Management Plan

This plan established the risk management activities to support the commercial release of Access 2 system software version 3.3. It includes a description of:

- responsibilities
- risk acceptability
- risk assessment activities
- verification activities
- risk management reviews, and
- the post-launch risk management plan

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6.8.6. Access 2 3.3 Software Testing and Software Validation Plan

This Software Testing and Software Validation Plan provided the guidance to execute the activities necessary to ensure the Access 2 system software version 3.3 design outputs met the requirements of the design change inputs and conformed to user needs and intended use. It includes a description of:

- unit test,
- integration test,
- verification testing,
- validation testing,
- Change Point Analysis
- deliverables, and
- acceptance criteria

6.9. Software Verification and Validation Testing

6.9.1. Test Objectives

The software verification and validation testing ensured that the Access 2 system software version 3.3 design outputs met the requirements of the design inputs and conformed to the user needs and intended use. The objectives of the testing were to:

- Verify design changes to the system software specified in the Access 2 3.3 Work Item Inclusion List
- Verify thermal software requirements
- Verify no unintended changes have been introduced
- Verify correct installation of system software for the Access 2
- Validate operation of the system software conforms to user needs and intended use

6.9.2. Software Test Items

The software items tested included:

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- Access 2 Software CD, Version 3.3: includes builds 1006 to 3013 containing:
  - PC System Software
  - Instrument System Software
- Windows XPe and Windows NT4

6.9.3. Test Documents

Table 11 lists the testing that was performed for software verification and validation.

Table 11: Software Test and Validation Documents

Document Description
Access 2 3.3 Unit Test Summary
Access 2 3.3 Integration Test Summary
Access 2 3.3 Software Testing And Software Validation Plan
Access 2 3.3 Software Testing And Software Validation Summary
Access 2 3.3 System Integration Software Testing Protocol
Access 2 3.3 System Integration Software Testing Report
Access 2 3.3 IVD System Integration Software Testing Protocol
Access 2 3.3 IVD System Integration Software Testing Report
Access 2 3.3 System Level Test Protocol
Access 2 3.3 System Level Test Report
Access 2 Software Verification Test Case Protocols
Access 2 Software Validation Test Case Protocols

6.9.4. Overview of Testing

The Access 2 3.3 Work Item Inclusion List, provided in Appendix 12, contains the detailed list of all functional changes approved for inclusion in the Access 2 system software version 3.3 release. There may be more than one work item to implement a feature. Test cases were developed and performed to verify and validate the work items. Software test procedures are comprised of multiple test cases. The test cases are designed by engineers who specialize in the functional area represented by the requirement. Test cases are formally reviewed and approved by a

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team consisting at a minimum of the Software Test Engineer and a Software Development Engineer with expertise in the functional area. The work items and applicable test cases associated with the changes for the thermal algorithm are traceable to the requirements documents as shown in the Thermal Algorithm Design Traceability Matrix. Other testing is traced to requirements and risks as shown in the Access 2 3.3 System Risk Assessment.

Investigation Use Only (IUO) integration builds were created, verified and validated in accordance to the plan and ahead of the IVD release build. An IVD build of the system software was created, tested and released with the final versions of the Help files and user interface language strings. The IVD build incorporated the un-modified source code used for the final IUO build, an updated installation program, a set of updated language string and Help files and removal of the IUO label. Integration testing activities completed for the IUO build were not repeated with the IVD build since no source code changes were introduced. The IVD testing included verification and validation testing for the NT and XPe console operating systems. One system software CD was created which auto-detects the operating system on which the software was installed and automatically installs the correct package for the targeted operating system. The installation software allows installation of the same system Software binary on either NT or XPe.

The software verification and validation activities included Code Reviews, Unit Test, Integration Test, Change Point Analysis, Software System Test (Verification) and Software Validation.

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6.9.5. Unit Test

Unit testing was performed by software developers on software units to ensure the software functions as designed. All new or modified software code was unit tested prior to being included in an integration or release build. It is the responsibility of the software developer to ensure that the unit testing executed is sufficient for the source code implemented. The unit test was reviewed in a formal team review. Reviewers ensured that the unit test covered the potential hazards, malfunctions and use errors. Details of the unit test are documented in the work items. The results of the Unit Test are provided in the Access 2 3.3 Unit Test Summary which is provided in Appendix 13.

6.9.6. Integration Test

Each work item resulting in a change to the system software was verified by execution of test cases to ensure functional integrity. Work item testing included specific testing to verify that all assay results were suppressed when outside of the instrument case temperature range and to verify that the algorithm is correctly applied. A technical peer review was performed for the test cases executed for testing of the work items. The test cases were documented in the work item record in TFS and the work item was closed. All test cases were executed successfully.

IUO software builds to be used internally and at clinical sites were completed and verified. Additional testing was performed on the IVD system software build to verify the updated Help and added language translations. Corresponding work items were created to handle their addition and verification. In addition the installation code was changed and verified to allow installing the same system software executable on either NT or XPe platforms. The source code to the system software was not modified in any way between the final IUO and IVD versions. The

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results of the integration test are provided in the Access 2 3.3 Integration Test Summary which is provided in Appendix 14.

6.9.7. Change Point Analysis

Change Point Analysis was an activity which was initiated before verification testing and stopped after the last software build. A Change Point Analysis Review was performed on each build used for testing purposes. It consisted of a Technical Peer Review held for the build to analyze the changes introduced into the new software build and the impact of these changes on scheduled verification activities. The review included at a minimum the Software Test Lead and/or Software Test Supervisor and Software Development. The purpose of the Change Point Analysis was as follows:

- Assessed readiness for system testing for approved features of the release
- Identified un-reviewed source code changes and determined appropriate action
- Identified source code changes that were either missing from the build or should not be part of the build
- Identified source code changes that impacted previously completed verification tasks
- Determined appropriate re-verification tasks

6.9.8. Software System Verification Testing

Software system verification testing was performed to ensure the software functions as designed. Specific software test procedures were selected to exercise areas affected by the design changes. The system verification testing incorporated the risks and hazards identified in each work item. The table below lists the required verification, the verification protocol, the justification for testing and the results of testing. The verification

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testing summarized in Table 12 is provided in the Access 2 3.3 Software Testing and Software Validation Plan and Summary which are provided in Appendices 15 and 16, respectively.

Table 12: Software System Verification Testing

Required Verification	Verification Protocol	Description	Result
IUO Build Software System Test			
Verify that all files on the Version 3.3 CD are identical to the Version 3.2 CD with the exception of the affected files as identified in the Work Items.	Install Shield Output Files Audit- Compare the Install Shield files Output from 3.3 with the Install Shield files Output from Version 3.2. and verify that all expected files are included in the build.	Verifies that all expected files are included in the build and that no unexpected files are included.	Passed
Qualification of daily builds used for formal testing	Test Case Work Item 37836 Access 2 Build Qualification Test Procedure	Verifies the daily build can be installed and that the software can execute representative assays to completion (with simulated RLU values) and a calibrator run.	Passed
Current functionality of system software	Test Case Work Item 85251 – Access 2 Results Testing for Quantitative, Qualitative, Semi-Qualitative and Confirmatory Assays	Verifies that the thermal algorithm implementation has not impacted other assay types. Perform test case TST1 (quantitative results).	Passed
Current functionality of system software	Test Case Work Item 84562 - Copy to Disk Regression Test	Verifies that the contents of the Diagnostics Copy to Disk are correct. Perform test case 1.	Passed
Instrument Temperature Acquisition	Test Case Work Item 85848 - Instrument Temperature Acquisition	Verifies that the instrument temperature is measured by the instrument and relayed to the user interface and that the system software accurately measures and calculates temperature values from the instrument sensor for use with the Algorithm.	Passed

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Table 12: Software System Verification Testing

Required Verification	Verification Protocol	Description	Result
Temperature Monitoring and Assigned Temperature Detection	Test Case Work Item 86262 - Temperature Monitoring and Assigned Temperature Determination	Verifies that the instrument regularly samples and time stamps instrument temperature throughout assay processing, creating a data list for each result and calibration. Each result is effectively associated with a list of paired temperatures and time stamps. The System Software stores each data list in the database.	Passed
Thermal Algorithm Implementation	Test Case Work Item 86263 – Thermal Algorithm Implementation	Verifies that the system software loads the algorithm from the APF into the system software database and calculates the adjusted result. The adjusted results are compared to the results independently calculated via a validated Excel spreadsheet. Discrete datasets are created to stress both instrument temperature and assay result boundary conditions.	Passed
Data Storage	Test Case Work Item 86264 - Data Storage of Thermal Information	Verifies that the System Software correctly stores the data in the System Software database. The required data stored includes the calibration temperature, the result temperature, the unadjusted result, the adjusted result, and the Algorithm used for calculations.	Passed
Test Result Reporting	Test Case Work Item 86265 - Test Result Reporting of Thermally Corrected Results	Verifies that the System Software accurately reports the adjusted result. The System Software can report results via the user interface display, printed result reports, electronically to the Laboratory Information System (LIS), or to a result data file.	Passed
Exercise the thermal adjustment algorithm in a range of unadjusted dose values	Test Case Work Item 94830 - Domain Check of Uncorrected Dose for Thermal Adjustment Calculation	Verifies that the System Software accurately reproduces the thermal algorithm function at the clinically significant range.	Passed
Systems Integration Assay testing of TnI for the implementation of the thermal	Access 2 3.3 System Integration Software Testing Protocol	Verifies the expected algorithm implementation and integration by exercising the algorithm in a system environment with wet	Passed (See section

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Table 12: Software System Verification Testing

Required Verification	Verification Protocol	Description	Result
algorithm for temperature adjustment and the new pipetting Cycle U command		assay reagents and dynamic temperature inputs. Also verifies the new pipetting Cycle "U" Command.	(6.9.9) below, System Integration Software Testing-IUO, for more details)
2nd IUO Build Software System Test			
Temperature Monitoring and Assigned Temperature Detection	Test Case Work Item 86262 - Temperature Monitoring and Assigned Temperature Determination	Verifies that the instrument regularly samples and time stamps instrument temperature throughout assay processing, creating a data list for each result and calibration. Each result is effectively associated with a list of paired temperatures and time stamps. The System Software stores each data list in the database.	Passed
IVD Build Specific Software System Test			
Verify that all files on the Version 3.3 CD are identical to the Version 3.2 CD with the exception of the affected files as identified in the Work Items.	Install Shield Output Files Audit- Compare the Install Shield files Output from 3.3 with the Install Shield files Output from Version 3.2 and verify that all expected files are included in the build. Platform: XPe	Verifies that all expected files are included in the build and that no unexpected files are included.	Passed
Verify that all files on the Version 3.3 CD are identical to the Version 2.8 CD with the exception of the affected files as identified in the Work Items.	Install Shield Output Files Audit- Compare the Install Shield files Output from 3.3 with the Install Shield files Output from Version 2.8 and verify that all expected files are included in the build. Platform: NT	Verifies that all expected files are included in the build and that no unexpected files are included.	Passed

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Table 12: Software System Verification Testing

Required Verification	Verification Protocol	Description	Result
Current functionality of system software	Test Case Work Item 84562 – Copy to Disk Regression Test Platform: NT and XPe	Verifies the contents of the Diagnostics Copy to Disk are correct for each scenario tested.	Passed
Current functionality of system software	Test Case Work Item 85251 – Access 2 Results Testing for Quantitative, Semi Quantitative, Qualitative and Confirmatory Assays Platform: NT	Verifies the input and output of Quantitative, Semi Quantitative and Qualitative Assays for both thermal and non-thermal controlled assays	Passed
Current functionality of system software	Test Case Work Item 112816 – Workgroup Test Case Platform: NT	Verifies the Access 2 workgroups behave as intended	Passed
Instrument Temperature Acquisition	Test Case Work Item 85848 - Instrument Temperature Acquisition Platform: NT	Verifies the instrument temperature is measured by the instrument and relayed to the user interface. The system software accurately measures and calculates temperature values from the instrument sensor for use with the Algorithm	Passed
Temperature Monitoring and Assigned Temperature Detection	Test Case Work Item 86262 - Temperature Monitoring and Assigned Temperature Detection Platform: NT	Verifies the instrument regularly samples and time stamps instrument temperature throughout assay processing, creating a data list for each result and calibration. Each result is effectively associated with a list of paired temperatures and time stamps. The System Software stores each data list in the database.	Passed

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Table 12: Software System Verification Testing

Required Verification	Verification Protocol	Description	Result
Thermal Algorithm Implementation	Test Case Work Item 86263 - Thermal Algorithm Implementation Platform: NT	Verifies that the system software loads the algorithm from the APF into the system software database and calculates the adjusted result. The adjusted results is compared to the results independently calculated via a validated Excel spreadsheet. Discrete datasets are created to stress both instrument temperature and assay result boundary conditions.	Passed
Data Storage	Test Case Work Item 86264 - Data Storage of Thermal Information Platform: NT	Verifies that the System Software correctly stores the data in the System Software database. The required data stored includes the calibration temperature, the result temperature, the unadjusted result, the adjusted result, and the Algorithm used for calculations.	Passed
Test Result Reporting	Test Case Work Item 86265 – Test Result Reporting of Thermally Corrected Results Platform: NT	Verifies that the System Software accurately reports the adjusted result. The System Software can report results via the user interface display, printed result reports, electronically to the Laboratory Information System (LIS), or to a result data file.	Passed
Systems Integration Assay testing of TnI for the implementation of the thermal algorithm for temperature adjustment and the new pipetting Cycle "U" command	Access 2 3.3 IVD System Integration Software Testing Protocol	Verifies the expected algorithm implementation and integration by exercising the algorithm in a system environment with wet assay reagents and dynamic temperature inputs. Also verifies the new pipetting Cycle "U" Command.	Passed (See section (6.9.10) below, System Integration Software Testing-IVD, for more details)

6.9.9. System Integration Software Testing- IUO Build

This testing verifies the capability of the Access 2 system software version 3.3 to:

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

- apply an algorithm to adjust the dose result for thermally sensitive assays, and
- the capability to run a "U" Command introduced in specific assay protocol files.

6.9.9.1.Testing Description

To verify that the application of the thermal algorithm and "U" Command were performed by the software as expected, multiple levels of the MORE Diagnostics Cardiac Quality Control material were tested with the AccuTnI assay on two Access 2 instruments. The Quality Control material is known to have a temperature dependent dose response in the absence of a thermal adjustment. The instrument ran in a thermal chamber at three temperature settings (18°C, 24°C, and 30°C). The adjusted results obtained from this testing were compared to results independently calculated via a validated Excel spreadsheet to determine if the thermal algorithm had been applied correctly. The acceptance criterion was that the thermally adjusted dose from the Access 2 instrument running system software version 3.3 must be identical to the adjusted dose as calculated by the Excel spreadsheet to within 2 decimal places (0.00). This testing demonstrated acceptable thermal monitoring functionality and the capability to apply the algorithm.

For the "U" Command, oscilloscope readings were monitored during the mixing cycle. The acceptance criterion was that the mixing frequency of the probe be maintained throughout the duration of the mixing cycle.

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6.9.9.2. Testing Results

The results of the thermal algorithm application testing are provided in Table 13. All thermally adjusted dose values for both Access 2 instruments for all samples tested were identical to the adjusted dose values calculated by the Excel spreadsheet to within 2 decimal places. The system integration software testing verified that the application of the thermal algorithm as implemented in the Access 2 system software version 3.3 performed as expected and met the acceptance criteria.

Table 13: Results of Comparison Testing- IUO

Sample	# Instruments	# Replicates per Instrument	Difference Between Independent and Instrument Corrected Dose = 0.00
Access 2 Instruments at 18°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 Instruments at 24°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 Instruments at 30°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed

The "U" Command testing met the acceptance criteria. The hardware signals monitored via an oscilloscope matched the expected waveforms. Results of this test demonstrated that the frequency of the mixing probe was maintained and consistent for the entire duration of the mixing cycle.

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This verification testing is provided in the Access 2 3.3 System Integration Software Testing Protocol and Report which are provided in Appendices 17 and 18 respectively.

6.9.10. System Integration Software Testing- IVD Build

Section 6.9.9, System Integration Software Testing, was repeated using the IVD release software 3.3. The IVD software release combined the single executable software for both Windows XPe and NT platforms onto a single CD to allow installation of the system software on either operating system.

The thermal algorithm application and "U" command testing was performed on four instruments, two with Windows NT and two with Windows XPe operating systems. The number of controls, the number of replicates, the temperatures and the acceptance criteria are the same as in the previous study with the IUO build software 3.3.

The results of the thermal algorithm application testing are provided in Table 14 below. All thermally adjusted dose values for both Access 2 instruments for all samples tested were identical to the adjusted dose values calculated by the Excel spreadsheet to within 2 decimal places (0.00). The system integration software testing verified that the application of the thermal algorithm as implemented in the Access 2 IVD system software version 3.3 performed as expected and met the acceptance criteria.

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Table 14: Results of Comparison Testing- IVD

Sample	# Instruments	# Replicates per Instrument	Difference Between Independent and Instrument Corrected Dose = 0.00
Access 2 NT Instruments at 18°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 XPe Instruments at 18°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 NT Instruments at 24°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 XPe Instruments at 24°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 NT Instruments at 30°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed
Access 2 XPe Instruments at 30°C			
QC1	2	10	Passed
QC2	2	10	Passed
QC3	2	10	Passed

The "U" Command testing met the acceptance criteria. The hardware signals monitored via an oscilloscope matched the expected waveforms. Results of this test demonstrated that the frequency of the mixing probe was maintained and consistent for the entire duration of the mix cycle.

The verification testing is provided in the Access 2 3.3 IVD System Integration Software Testing Protocol and Report which are provided in Appendices 19 and 20 respectively.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

6.9.11. Software System Level Test

The Access 2 3.3 System Software Change Risk Assessment called for system level testing of the Access 2 3.3 software. The prescribed verification protocol used multiple assays to mitigate risk that the cumulative implementation of the software features in system software version 3.3 may adversely affect the Access 2 instrument on the system level to generate correct results.

The testing consisted of a selected mix of assays representing a range of assay process variables (format, different incubation times, sample volume, 1 step, 2 step, competitive, sequential and dilution). The assays tested are listed in Table 15.

Table 15: System Level Testing Assays

Assay	Characteristics
Alpha-fetoprotein (AFP)	One step sandwich assay Short incubation length assay Makes sample dilution in RV
Folate	Sequential competitive assay Medium incubation length assay
Free T4	Two step competitive assay Medium incubation length assay
Hybritech PSA	One step sandwich assay Medium incubation length assay
Troponin IUO	Piggyback sandwich Tests new thermal algorithm data reduction Short incubation length assay Tests new "U" assay processing command
Total IgE	Two step sandwich assay Longest incubation length assay
Total T4	Single step competitive assay Medium incubation length assay
Hybritech Free PSA	One step sandwich assay Medium incubation length assay
Diluted Total βhCG	Dilution assay Short incubation length assay One Step sandwich assay

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Six runs, with 5 replicates of three QC samples per run, were performed on each assay type for a total of 90 replicates per assay type. Testing was performed on two Access 2 instruments. The acceptance criteria were:

- The overall QC sample precision must conform to the criteria listed in the specific assay specifications, and
- The mean QC sample results must fall within stated ranges.

The results of the testing are summarized in Table 16 and Table 17. All testing passed the acceptance criteria. The cumulative implementation of software features in Access 2 3.3 software did not impact the ability of the system to generate precise and accurate assay results. The testing is provided in Access 2 3.3 Software System Level Test Protocol and Report which are provided in Appendices 21 and 22 respectively.

Table 16: System Level Testing Precision Results

Assay	QC Level	Precision Acceptance Criteria	Result Total Precision		Precision Pass/Fail
			Instrument 500537	Instrument 5007295	
Alpha Fetoprotein (AFP)	1	CV ≤8%	6.7% CV	2.7% CV	Pass
	2	CV ≤8%	5.2% CV	3.1% CV	Pass
	3	CV ≤8%	5.8% CV	2.0% CV	Pass
Folate	1	CV ≤10%	2.2% CV	4.0% CV	Pass
	2	CV ≤10%	2.8% CV	2.4% CV	Pass
	3	CV ≤10%	2.1% CV	2.0% CV	Pass
Free T4	1	CV ≤10%	2.8% CV	4.2% CV	Pass
	2	CV ≤10%	2.7% CV	3.0% CV	Pass
	3	CV ≤10%	3.0% CV	3.4% CV	Pass
Hybritech PSA	1	SD ≤0.1 ng/mL	0.012 ng/mL SD	0.013 ng/mL SD	Pass
	2	CV ≤7%	2.8% CV	2.9% CV	Pass
	3	CV ≤7%	3.0% CV	2.9% CV	Pass
Troponin IUO	1	SD ≤.0084 ng/mL	0.004 ng/mL SD	0.002 ng/mL SD	Pass
	2	CV ≤8%	3.5% CV	2.5% CV	Pass
	3	CV ≤8%	3.2% CV	2.4% CV	Pass
Total IgE	1	CV ≤10%	4.0% CV	4.6% CV	Pass
	2	CV ≤10%	4.5% CV	6.5% CV	Pass
	3	CV ≤10%	5.4% CV	6.3% CV	Pass
Total T4	1	CV ≤7%	3.6% CV	5.1% CV	Pass
	2	CV ≤7%	4.4% CV	4.5% CV	Pass
	3	CV ≤7%	2.7% CV	7.0% CV	Pass
Hybritech	1	SD ≤.07 ng/mL	0.010 ng/mL SD	0.008 ng/mL SD	Pass

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Assay	QC Level	Precision Acceptance Criteria	Result Total Precision		Precision Pass/Fail
			Instrument 500537	Instrument 5007295	
Free PSA	2	CV ≤7%	2.9% CV	3.5% CV	Pass
	3	CV ≤7%	2.8% CV	4.1% CV	Pass
Diluted Total βhCG2	1	CV ≤10%	3.5% CV	3.9% CV	Pass
	2	CV ≤10%	2.1% CV	3.8% CV	Pass
	3	CV ≤10%	2.7% CV	4.4% CV	Pass

Table 17: System Level Testing Accuracy Results

Assay	QC Level	Accuracy Specification (Stated Dose Range)	Result Total Accuracy		Accuracy Pass/Fail
			Instrument 500537	Instrument 5007295	
Alpha Fetoprotein	1	28.7 - 39.6 ng/mL	36.1 ng/mL	33.4 ng/mL	Pass
	2	99.8 - 138 ng/mL	125 ng/mL	115 ng/mL	Pass
	3	229 - 317 ng/mL	286 ng/mL	264 ng/mL	Pass
Folate	1	2.88 - 4.00 nmol/L	3.37 nmol/L	3.23 nmol/L	Pass
	2	9.52 - 13.2 nmol/L	10.8 nmol/L	10.8 nmol/L	Pass
	3	11.5 - 15.8 nmol/L	13.0 nmol/L	12.8 nmol/L	Pass
Free T4	1	0.61 - 0.85 ng/dL	0.78 ng/dL	0.70 ng/dL	Pass
	2	1.67 - 2.31 ng/dL	2.06 ng/dL	1.94 ng/dL	Pass
	3	2.95 - 4.07 ng/dL	3.72 ng/dL	3.49 ng/dL	Pass
Hybritech PSA	1	0.27 - 0.39 ng/mL	0.34 ng/mL	0.36 ng/mL	Pass
	2	3.22 - 4.46 ng/mL	3.86 ng/mL	4.11 ng/mL	Pass
	3	22.1 - 30.6 ng/mL	26.2 ng/mL	28.4 ng/mL	Pass
Troponin IUO	1	0.035 - 0.079 ng/mL	0.050 ng/mL	0.054 ng/mL	Pass
	2	0.842 - 1.163 ng/mL	0.955 ng/mL	0.920 ng/mL	Pass
	3	12.402 - 17.127 ng/mL	14.154 ng/mL	13.788 ng/mL	Pass
Total IgE	1	48.0 - 66.4 IU/mL	59.2 IU/mL	58.1 IU/mL	Pass
	2	63.8 - 89.3 IU/mL	79.9 IU/mL	77.6 IU/mL	Pass
	3	86.4 - 119 IU/mL	103 IU/mL	106 IU/mL	Pass
Total T4	1	5.92 - 8.16 µg/dL	7.13 µg/dL	7.05 µg/dL	Pass
	2	8.65 - 11.9 µg/dL	10.4 µg/dL	10.1 µg/dL	Pass
	3	12.2 - 16.8 µg/dL	14.8 µg/dL	14.5 µg/dL	Pass
Hybritech Free PSA	1	0.15 - 0.19 ng/mL	0.17 ng/mL	0.17 ng/mL	Pass
	2	1.59 - 2.19 ng/mL	1.97 ng/mL	1.94 ng/mL	Pass
	3	11.2 - 15.4 ng/mL	13.7 ng/mL	13.6 ng/mL	Pass
Diluted Total βhCG2	1	7716 - 11348 mIU/mL	9286 mIU/mL	9374 mIU/mL	Pass
	2	28280 - 39360 mIU/mL	32524 mIU/mL	32810 mIU/mL	Pass
	3	49055 - 72396 mIU/mL	59696 mIU/mL	59679 mIU/mL	Pass

6.9.12. Software Validation

Software validation testing was performed to ensure the software functions correctly for its intended use. The validation tested the software

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

as part of the entire system to determine whether it met the intended use of the end-user. The Software System Test incorporated the risks and hazards identified in each work item.

IUO Access 2 system software version 3.3 (XPe) was provided prior to final IVD release. The IVD version of the System Software was created after the IUO was put in use. The IUO Software was used for generating analytical and clinical data to support this AccuTnI 510(k).

Table 18 lists the required validation and outcomes for the IUO and IVD system software builds.

The validation testing summarized in Table 18 is provided in the Access 2 3.3 Software Testing and Software Validation Plan and Summary which are provided in Appendices 15 and 16 respectively.

Table 18: Software Validation Testing

Required Validation	Validation Protocol	Description	Result
IUO Build Specific Software Validation			
Current functionality	NexStep Integration Test Procedure Platform: XPe	The NexStep Integration Test Procedure exercises broad operation and functionality of the major functions and features in the system. This demonstrates that the system software meets the intended use of the user.	Passed

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 18: Software Validation Testing

Required Validation	Validation Protocol	Description	Result
User Scenario	Test Case WI 47188 Community Hospital User Scenario – Access 2 Platform: XPe	Maximizes system usage based on how a community hospital will use the software, by broadening the exercising of features to gain confidence in the System Software. This increases the total number of run hours and samples/reps processed. -Test on a Access 2 -5 runs of approximately 137 replicates per run. -Assay mix: 12 – 15 assays (including thermally-sensitive AccuTnI) similar to the way that a customer runs.	Passed
Installation of the Access 2 3.3 System Software	Selected Access 2 3.3 Software Install Test scenarios	Verifies operation and functionality of all major functions and features to demonstrate that unintended changes have not been introduced.	Passed
2nd IUO Build Specific Software Validation			
Current functionality	NexStep Integration Test Procedure Platform: XPe	The NexStep Integration Test Procedure exercises broad operation and functionality of the major functions and features in the system. This demonstrates that the system software meets the intended use of the user.	Passed
Installation of the Access 2 3.3 System Software	Selected Access 2 3.3 Software Install Test scenarios Platform: XPe	Verifies operation and functionality of all major functions and features to demonstrate that unintended changes have not been introduced.	Passed
IVD Build Specific Software Validation			
Current functionality	NexStep Integration Test Procedure Platform: NT	The NexStep Integration Test Procedure exercises broad operation and functionality of the major functions and features in the system. This demonstrates that the system software meets the intended use of the user.	Passed

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 18: Software Validation Testing

Required Validation	Validation Protocol	Description	Result
Current functionality	NexStep Integration Test Procedure Platform: XPe	The NexStep Integration Test Procedure exercises broad operation and functionality of the major functions and features in the system. This demonstrates that the system software meets the intended use of the user.	Passed
Installation of the Access 2 3.3 System Software	Selected Access 2 3.3 Software Install Test scenarios Platform: XPe and NT	Verifies operation and functionality of all major functions and features to demonstrate that unintended changes have not been introduced.	Passed
User Scenario	Test Case WI 47188 Community Hospital User Scenario – Access 2 Platform: XPe and NT	Maximizes system usage based on how a community hospital will use the software, by broadening the exercising of features to gain confidence in the System Software. This increases the total number of run hours and samples/reps processed. -Test on a Access 2 -7 runs of approximately 137 replicates per run (each run equals an 8 hour shift) -Assay mix: 12 – 15 assays (including thermally-sensitive AccuTnI) similar to the way that a customer runs.	Passed

6.9.13. Conclusion

All verification and validation testing met acceptance criteria. All tests were executed to completion with only one variance from a test procedure for Test Case 86264 Data Storage of Thermal Information which is described in the Access 2 3.3 Software Testing and Software Validation Summary. The identified variance did not affect accuracy of verification or validation.

All risks identified in the Access 2 3.3. Software Change Risk Assessment were mitigated through verification and validation testing and the testing

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is traced in the Verification of Risk Control Measures table in the Access 2 3.3 Software Testing and Software Validation Summary.

Additional work items were created for issues identified during verification and validation testing. These work items were corrected, verified and closed in software release 3.3 or deferred to a future release. Work items generated during formal testing were closed with code correction, closed with no code change or deferred to a future release and listed in the unresolved anomalies list. The additional work items are described in the Access 2 3.3 Software Testing and Software Validation Summary.

6.10. Software Revision History

AccuTnI will be commercialized with Access 2 system software version 3.3 or higher. An annotated revision history log with the last FDA reviewed version and subsequent revision levels identified for Access 2 is provided in Table 19.

Table 19: Revision History

Software Revision Level	Date of Release to Manufacturing	Description	FDA Document Number
2.4	August 2005	Most recent FDA reviewed version	P980041/S008

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 19: Revision History

Software Revision Level	Date of Release to Manufacturing	Description	FDA Document Number
2.5	May 2008	• Changes to the wash protocol to support both Wash Buffer and the new Wash Buffer II • Added support for 5 new primary tubes • Add Ferritin ratio capability to Access 2 • Add diagnostic capability for internal reagent QC • Changed association of user units with sample fluid type to no longer use the user unit for the default fluid type but rather use the user unit for the fluid type associated with the sample when performing an LIS Host Query. • Implemented support for Multi Network Card.	Not Applicable
2.6	October 2008	• Not distributed to customers • Changes to prevent APF update failures • Added capability to monitor sample carousel position errors • Changes to support internal tool for automated electronic data collection • Utility assay will run with defective vacuum pump • Exclude Obstruction Detection from Dilution Vessel	Not Applicable
2.7	January 2009	• Not distributed to customers • Additional modifications to sample carousel position monitoring • Enhancements to internal tool for automated electronic data collection • Fatal System SW error intermittent during utility assay • Diagnostic copy to disk performance issues	Not Applicable
2.8	March 2009	Additional modifications to sample carousel position monitoring	Submitted for Access Hybritech p2PSA P980041/S009 (under review)

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 19: Revision History

Software Revision Level	Date of Release to Manufacturing	Description	FDA Document Number
2.8.1*	March 2011	• Not distributed to customers • Added capability to log instrument case temperature	Not Applicable
3.0	November 2009	Conversion to Windows XPe	Not Applicable
3.1	February 2010	Changes to support new Iowa CPU	Not Applicable
3.2	December 2010	Changes to support new Iowa CPU	Not Applicable
3.3	Pending	• Added capability to apply a temperature based algorithm to assay results • Suppress results for all assays if the case temperature is outside the 18°C to 36 °C range. • Added capability to run "U" Command	Pending (this submission)

*This branch was specific to NT only. Changes included in this branch were not carried forward.

A side by side comparison of software version 2.4 to the planned release version for Access 2 software 3.3, with an explanation of how the differences do or do not impact safety and effectiveness, are described in Table 20.

Table 20: Comparison to Reviewed Version

Item	Software Functionality in Version 2.4	Change	Software Revision Level in Which Change was Implemented	Impact on Safety and Effectiveness
1	Supports Access Wash Buffer	Changes to the wash protocol to support both Wash Buffer and the new Wash Buffer II	2.5	Implementation of a wash protocol that is equivalent for both wash buffers does not impact safety and effectiveness
2	Supports set number of validated primary tubes	Added support for 5 new primary tubes	2.5	Addition of sample tubes does not impact safety and effectiveness
3	Logarithmic computational functionality not supported	Added logarithmic computational functionality	2.5	Adding computational functionality does not impact safety and effectiveness

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 20: Comparison to Reviewed Version

Item	Software Functionality in Version 2.4	Change	Software Revision Level in Which Change was Implemented	Impact on Safety and Effectiveness
4	Reporting units associated with custom fluid type is set after the first usage of the sample	Reporting units associated with custom fluid type is set before the first usage of the sample	2.5	Applying reporting units prior to first usage of custom fluid type improves safety and effectiveness
5	Support for one Network Interface Card	Support for multiple Network Interface Cards	2.5	Implementation of capability for multiple network connections does not impact safety and effectiveness
6	Possible for APF update to fail	Changes to prevent APF update failures	2.6	Improving APF update process robustness improves safety and effectiveness
7	Sample carousel could be moved without notice	Added capability to monitor sample carousel position errors	2.6	Implementing position monitoring improves safety and effectiveness
8	Internal tools require manual data collection	Changes to support internal tool for automated electronic data collection	2.6	Addition of data collection tool does not impact safety and effectiveness
9	Utility Assay starts with insufficient vacuum	System goes to Not Ready Mode if Utility Assay detects insufficient vacuum	2.6	Monitoring of vacuum before the utility assay does not impact safety and effectiveness
10	Instrument checks for obstruction in dilution vessel	Obstruction detection is disabled for dilution vessel	2.6	Removal of unnecessary feature does not impact safety and effectiveness
11	Sample carousel position monitoring needs refinement	Additional modifications to sample carousel position monitoring	2.7	Implementing position monitoring improves safety and effectiveness
12	Automated electronic data collection needs refinement	Enhancements to internal tool for automated electronic data collection	2.7	Data collection tool does not impact safety and effectiveness

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Table 20: Comparison to Reviewed Version

Item	Software Functionality in Version 2.4	Change	Software Revision Level in Which Change was Implemented	Impact on Safety and Effectiveness
13	Vacuum verification needs refinement	Additional modifications to vacuum verification during Utility Assay	2.7	Monitoring of vacuum before the utility assay does not impact safety and effectiveness
14	Sample carousel position monitoring needs refinement	Additional modifications to sample carousel position monitoring	2.8	Implementing position monitoring improves safety and effectiveness
15	Access 2 PC console operates on Windows NT platform	Access 2 PC console operates on Windows XPe platform	3.0	Change of PC console operating system is an obsolescence issue and does not impact safety and effectiveness
16	Database backup is performed on Tape media	Support Flash drive for Backup of database	3.0	Backup location does not impact safety and effectiveness
17	Derived results cannot contain the same assay name more than once in a formula	The system logic can evaluate derived results with the same assay specified multiple times	3.0	Improved evaluation of derived results does not impact safety and effectiveness
18	Instrument does not support new IOWA CPU	Instrument supports new IOWA CPU	3.1	Support for new CPU is an obsolescence issue and does not impact safety and effectiveness
19	Instrument does not support new IOWA CPU	Additional changes Instrument supports new IOWA CPU	3.2	Support for new CPU is an obsolescence issue and does not impact safety and effectiveness
20	System cannot apply temperature adjustment algorithms to assay results.	Added capability to apply a temperature based algorithm to assay results	3.3	Implementing temperature based algorithm to assay results improves safety and effectiveness

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 20: Comparison to Reviewed Version

Item	Software Functionality in Version 2.4	Change	Software Revision Level in Which Change was Implemented	Impact on Safety and Effectiveness
21	System does not monitor instrument case temperature during assay processing	Suppress results for all assays if the case temperature is outside the 18°C to 36 °C range	3.3	Implementing results suppression when the case temperature is outside the 18°C to 36 °C range improves safety and effectiveness for thermally sensitive assays
22	Instrument software does not have an option to Lock the mixing frequency when mixing particles.	Implement "U" command that locks the mixing frequency.	3.3	Ensuring consistent frequency during particle mixing improves safety and effectiveness.

6.11. Unresolved Anomalies

Anomalies identified during development, integration testing, system testing, software validation, and/or throughout the software life cycle are documented via a defined software problem resolution process or through Work Items stored in Microsoft Team Foundation Server. A triage team evaluates each Work Item in order to assess its severity, root cause, impact on the safety and effectiveness of the product and possible workarounds. No unresolved anomalies remain that affect safety or effectiveness of the product. The list of unresolved anomalies is provided in Appendix 23.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

7.0 Hardware

7.1. Hardware Design Changes

In order to implement the software thermal algorithm, the following specifications were changed for the Access 2 instrument:

- Labeling of the ambient operating temperature range was changed to 18°C to 28°C.
- Labeling of the instrument case temperature range (internal instrument temperature) of 18°C to 36°C was added.
- The requirement to accurately measure the instrument case temperature within ±1.0°C was implemented and verified.

No physical components or modules were altered as part of these design changes. Only the specifications for existing hardware and system components were modified.

7.2. Hardware Verification

7.2.1. Verification of the Temperature Measurement Accuracy of ±1.0 °C

In order to ensure proper dose adjustment by the thermal algorithm and appropriate assay result suppression, the instrument case temperature (internal instrument temperature) measurement system must be accurate (within ±1.0°C).

The instrument case temperature measurement system consists of two components: the case temperature sensor (thermistor), and the thermal circuit. The accuracy specification for the overall measurement system (±1.0°C) is verified by imposing specifications on each of these two components, and performing 100% verification that each component meets its corresponding specification. Figure 3 illustrates the

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

measurement system, its component parts, and the associated specifications and verification methods.

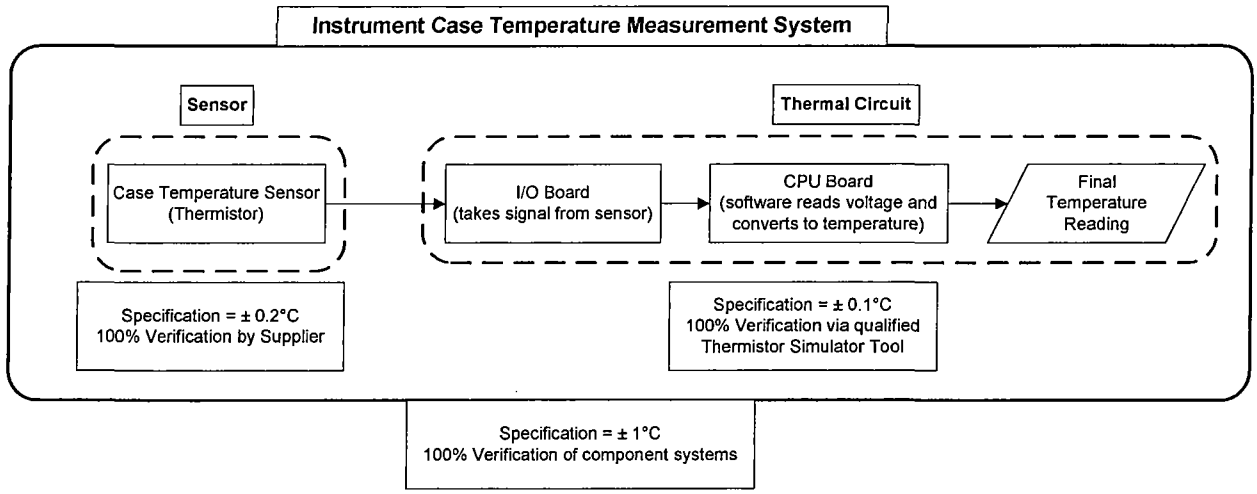

Figure 3: Instrument Case Temperature Circuit

The case temperature sensor (thermistor) is the critical hardware component used to detect small changes in temperature, and has an accuracy specification of ±0.2°C. This specification of ±0.2°C was 100% verified by the supplier. Manufacturing release procedures for new instruments ensure that verified thermistors are installed.

The thermal circuit consists of the hardware and software used to convert the thermistor output signal to a final temperature reading. The thermal circuit was 100% verified to a specification of ±0.01 via manufacturing release procedures for new instruments.

7.2.2. Verification of the Instrument Operating Temperature Range of 18°C to 28°C (ambient) and 18°C to 36°C (instrument case temperature)

Verification testing provided objective evidence that the Access 2 instrument is capable of operating within its specified operating

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

temperature ranges. This testing verified that the instrument's sub-assembly temperature control zones remained within their specified temperature ranges:

- The temperature of the incubator walls was controlled to 36.43°C ±0.3°C
- The chemiluminescent substrate was delivered at 36.43°C ±0.3°C
- Temperature of the substrate incubation portion of the wash wheel was controlled to 36.43°C ±0.3°C

The software monitors and produces an error flag if any of these temperature control zones are outside of these ranges. Verification acceptance criteria stated that no results suppression or temperature error flagging could occur within the tested samples due to out-of-specification temperature zones, throughout the duration of the test run.

Five Access 2 instruments of varying age (manufactured in 2000 through 2011) were each tested at five temperatures settings (18°C, 20.5°C, 23°C, 25.5°C, 28°C), under representative run conditions. There were no thermal flags or result suppression in the testing.

All Instruments at all temperatures met the acceptance criteria. The Thermal Control Hardware Verification Plan and Report are provided in the Appendices 24 and 25 respectively.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

8.0 Analytical Performance

Analytical performance of the AccuTnI assay was assessed through a series of studies on Access 2 instruments with Access 2 system software version 3.3 installed, which incorporated the thermal algorithm. As previously described in this submission, this thermal algorithm adjusts the result dose to mitigate the ambient temperature sensitivity of the AccuTnI assay.

- All studies were conducted at normal laboratory conditions (NLC). NLC was not a predetermined or controlled temperature, but rather, the actual recorded temperatures that occurred in the laboratory on the day(s) of the study.
- Selected studies were conducted at two additional controlled temperature conditions of 18°C and 28°C, representing laboratory conditions operating at the extremes of the recommended system and AccuTnI operating environment.
- When applicable, the studies performed at NLC, 18°C, and 28°C were performed according to protocols based on the Clinical and Laboratories Standards Institute (CLSI) standards. In the section descriptions below, these are referred to as "standardized studies".
- Selected studies were also conducted at up to six variable temperature conditions, spanning the range of 18°C and 28°C, representing laboratory conditions where temperature fluctuations may occur, which could influence AccuTnI results. In these studies, the data collected at all temperatures was combined for analyses. In the section descriptions below, these are referred to as "multi-temperature studies".
- In addition, for certain studies, further statistical analysis was conducted on the combined data collected from different temperatures,

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

to confirm between-temperature consistency and effectiveness of the thermal algorithm. In the section descriptions below, these are referred to as "cross-temperature analyses".

An overview of the analytical testing is provided Table 21. More detailed descriptions of the individual studies, data analysis, acceptance criteria, and results are provided in the text immediately following the table.

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Table 21: AccuTnI Analytical Performance Section Summary

Study	510(k) Section	18°C Testing	NLC Testing	28°C Testing	Multi-Temperature Testing
Limit of Blank	**8.1**	One EP17-A study	One EP17-A study	One EP17-A study	One study across six temperature set points
		Additional cross-temp statistical analysis of three EP17-A studies			
Limit of Detection	**8.2**	One EP17-A study	One EP17-A study	One EP17-A study	One study across six temperature set points
		Additional cross-temp statistical analysis of three EP17-A studies			
Limit of Quantitation	**8.3**	Three EP17-A studies	Three EP17-A studies	Three EP17-A studies	One study across six temperature set points. Additional cross-temp statistical analysis.
		Additional cross-temp statistical analysis of nine EP17-A studies			
Precision	**8.4**	One EP5-A study	One EP5-A study	One EP5-A study	One study across six temperature set points. Additional multi-temp statistical analysis.
Linearity	**8.5**	Four EP6-A studies	Four EP6-A studies	Four EP6-A studies	[redacted]
High Dose Hook Effect	**8.6**	[redacted]	One Study	[redacted]	[redacted]
Reagent pack real time stability	**8.7**	[redacted]	One Study	[redacted]	[redacted]
Reagent open pack stability		[redacted]	One Study	[redacted]	[redacted]
Stored calibration curve stability		[redacted]	One Study	[redacted]	[redacted]
Calibrator real time stability		[redacted]	One Study	[redacted]	[redacted]
Calibrator open vial stability		[redacted]	One Study	[redacted]	[redacted]
Interference and Analytical Specificity	**8.8**	One EP7-A2 study	One EP7-A2 study	One EP7-A2 study	[redacted]
Cross-reactivity	**8.9**	One EP7-A2 study	One EP7-A2 study	One EP7-A2 study	[redacted]
Sample Matrix Comparison	**8.10**	One study	One study	One study	[redacted]
HAMA / Heterophile	**8.11**	[redacted]	One study	[redacted]	[redacted]
Thermal Sensitivity – Robustness	**8.12**	[redacted]	[redacted]	[redacted]	One study across six temperature set points

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Table 21: AccuTnI Analytical Performance Section Summary

Study	510(k) Section	18°C Testing	NLC Testing	28°C Testing	Multi-Temperature Testing
Thermal Sensitivity – Impact on Low Dose Concordance / Agreement	**8.13**	[redacted]	[redacted]	[redacted]	One study across six temperature set points
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison	**8.14**	One study comparing results at 18°C, 23°C, and 28°C			[redacted]

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8.1. Limit of Blank (LoB)

Limit of Blank is defined as the highest measurement result that is likely to be observed (with a stated probability) for a blank (or zero analyte-containing) sample. Four laboratory studies were conducted to evaluate LoB for the AccuTnI assay on the Access 2 instrument.

Three standardized studies based on CLSI EP17-A were conducted. Each study was performed at one of three ambient temperature conditions (see Section 8.1.1). The fourth was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C (see Section 8.1.2).

Additional statistical analysis was conducted on the pooled data from the standardized studies to assess the impact of temperature on Limit of Blank (see Section 8.1.3).

8.1.1. Standardized LoB Study

Study Description: This LoB study was performed according to a protocol based on CLSI EP17-A using the AccuTnI S0 calibrator (zero analyte), which is a synthetic matrix buffer (buffered bovine serum albumin). Thirteen replicates of the zero analyte sample were tested in each of 12 total runs, using three instruments, two reagent lots, and two calibrator lots. This study was conducted three times, once at each of the following three ambient temperature conditions: 18 ±2°C, 28 ±2°C, and NLC (measured temperatures ranged from 24 to 25°C). A calibration curve was generated with each run.

Data Analysis: The signal generated (relative light units or RLU) for all zero analyte replicates were centered around the zero calibrator signal for

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each instrument and reagent lot. The one-sided, upper 95th percentile of the resultant zero analyte results was calculated as the estimated LoB. The 97.5% upper confidence limit of this estimate was calculated for each temperature condition and was used as the established LoB.

Acceptance Criteria: Per the AccuTnI Design Inputs, LoB must be ≤0.010 ng/mL.

Results: Results are provided in Table 22 below.

Table 22: Standardized Study LoB Results

Condition	Estimated LoB (ng/mL)	Established LoB (ng/mL)	Number of Replicates†
18°C	0.002	0.004	143
28°C	0.002	0.004	156
NLC (24.2 – 25.1°C)	0.002	0.003	156

† Per EP17-A, a minimum of 60 replicates are required to establish LoB.

Standardized LoB Study Conclusion: The LoB for the Access AccuTnI assay is 0.004 ng/mL. This meets the acceptance criteria of ≤0.010 ng/mL.

8.1.2. Multi-Temperature Study (Thermal Sensitivity – Impact on LoB)

Study Description: The purpose of this study was to confirm that change in ambient temperature does not impact the Limit of Blank. The AccuTnI S0 calibrator (zero analyte), which is a synthetic matrix of buffered bovine serum albumin, was the sample for this study. Thirteen replicates of the zero analyte sample were tested in each run. A total of 12 runs were completed using three instruments, two reagent lots, and two calibrator lots at the following ambient temperature conditions:

- Two runs at 18 ±2°C
- Two runs at 20 ±2°C
- Two runs at 22 ±2°C
- Two runs at 24 ±2°C

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- Two runs at 26 ±2°C
- Two runs at 28 ±2°C

A calibration curve was generated with each run at each temperature.

Data Analysis: All results at all temperatures were combined for this analysis. The signal generated (relative light units or RLU) for all zero analyte replicates were centered around the zero calibrator signal for each instrument and reagent lot. The one-sided, upper 95th percentile of the resultant zero analyte results was calculated as the estimated LoB. The 97.5% upper confidence limit of this estimate was calculated for each temperature condition and was used as the established LoB.

Acceptance Criteria: Per the AccuTnI Design Inputs, LoB must be ≤0.010 ng/mL.

Results: Results are provided in Table 23 below.

Table 23: Multi-Temperature LoB Results

Statistic	Estimated LoB (ng/mL)	Established LoB (ng/mL)	Number of Replicates
Limit of Blank across temperatures	0.002	0.003	163

Multi-Temperature LoB Study Conclusion: The multi-temperature study confirms the results obtained in the standardized study and supports the conclusion that the Limit of Blank for the Access AccuTnI assay is ≤0.010 ng/mL and is unaffected by changes in ambient temperatures across the range of 18°C to 28°C.

8.1.3. Cross-Temperature LoB Analysis

Study Description: The purpose of this analysis was to demonstrate that there is no significant difference in LoB when the assay is used under

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varying ambient temperature conditions. Statistical analysis was performed using data collected during the standardized LoB study described above.

Data Analysis: The difference between each of the established LoB values in each of the three studies was calculated, and the maximum difference observed was compared to the acceptance criteria.

Acceptance Criteria: Per the AccuTnI Design Inputs, the LoB for all studies at all temperatures must be within 0.010 ng/mL of each other.

Results: Results are provided in Table 24 below.

Table 24: Cross Temperature LoB Results

Condition	Established LoB (ng/mL)	Maximum Difference (ng/mL)
18°C	0.004	0.001
28°C	0.004	
NLC (24.2 – 25.1°C)	0.003	

Cross-Temperature LoB Analysis Conclusion: The acceptance criteria for this analysis have been met, which demonstrates that the LoB for the AccuTnI assay on the Access 2 instrument is not affected by variations in ambient temperatures between 18°C and 28°C.

8.1.4. Limit of Blank Conclusion

The standardized LoB studies established that the LoB is 0.004 ng/mL, and meets the acceptance criteria of ≤0.010 ng/mL. The multi-temperature study confirms that LoB is <0.010 ng/mL and the statistical analysis confirms that LoB is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.

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8.2. Limit of Detection (LoD)

Limit of Detection (LoD) is defined as the lowest amount of analyte in a sample that can be detected with 95% probability. Four laboratory studies were conducted to evaluate LoD for the AccuTnI assay on the Access 2 instrument.

Three standardized studies based on CLSI EP17-A were conducted. Each study was performed at one of three ambient temperature conditions (see Section 8.2.1). The fourth was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C (see Section 8.2.2).

Additional statistical analysis was conducted on the pooled data from the standardized studies to assess the impact of temperature on the Limit of Detection (see Section 8.2.3).

8.2.1. Standardized LoD Study

Study Description: This study was performed according to a protocol based on CLSI EP17-A using five samples with very low levels of troponin I. Samples were prepared from a high lithium heparin plasma sample spiked at different levels into a normal lithium heparin plasma pool; resulting levels ranged from approximately 0.010 ng/mL to 0.070 ng/mL. Each sample was tested in replicates of three for each run. A total of 12 runs were performed on three instruments with two reagent lots and two calibrator lots per instrument at each of three ambient temperature conditions: 18 ±2°C, 28 ±2°C, and NLC (measured temperatures ranged from 24°C to 25°C). A calibration curve was generated with each run.

Data Analysis: To calculate LoD, each within-run standard deviation was multiplied by a constant determined per CLSI EP17-A, and was added to the LoB estimate. To calculate the upper boundary each within-run

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standard deviation was multiplied by a constant and added to the upper 97.5% confidence limit of LoB.

Acceptance Criteria: Per the AccuTnI Design Inputs, LoD must be ≤0.030 ng/mL.

Results: Results are provided in Table 25 below.

Table 25: Standardized Study LoD Results

Condition	Calculated LoD (ng/mL)	LoD Upper Boundary (ng/mL)
18°C	0.004	0.006
28°C	0.008	0.009
NLC (24°C to 25°C)	0.005	0.005

Standardized LoD Study Conclusion: The LoD for the Access AccuTnI assay is 0.009 ng/mL. This meets the acceptance criteria of ≤0.030 ng/mL.

8.2.2. Multi-Temperature Study (Thermal Sensitivity – Impact on LoD)

Study Description: The purpose of this study is to confirm that change in ambient temperature does not impact the Limit of Detection. Five samples were prepared from a high lithium heparin plasma sample spiked at different levels into a normal lithium heparin plasma pool; levels ranged from approximately 0.010 ng/mL to 0.070 ng/mL. Each sample was tested in replicates of three for each run. A total of 12 runs were completed using three instruments, two reagent lots, and two calibrator lots at the following ambient temperature conditions:

- Two runs at 18 ±2°C
- Two runs at 20 ±2°C

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- Two runs at 22 ±2°C
- Two runs at 24 ±2°C
- Two runs at 26 ±2°C
- Two runs at 28 ±2°C.

A calibration curve was generated with each run at each temperature.

Data Analysis: All results at all temperatures were combined for this analysis. Each of the variance components was determined using an ANOVA for each sample and converted to standard deviation (SD). In this analysis, total standard deviation (including within run, between run, and between temperature precision) was used to calculate LoD. This represents a more conservative LoD estimate versus a standard LoD analysis which would typically use only within-run variability. To calculate LoD, each total standard deviation was multiplied by a constant determined per CLSI EP17-A, and was added to the LoB estimate. To calculate the upper boundary of LoD, each total standard deviation was multiplied by a constant and added to the upper 97.5% confidence limit of LoB.

Acceptance Criteria: Per the AccuTnI Design Inputs, the between-temperature variability for each sample must be less than the precision acceptance criteria (SD ≤0.0084 ng/mL at concentrations ≤0.105 ng/mL). In addition, using overall variability for each sample, the calculated LoD must be ≤0.030 ng/mL.

Results: Results are provided in Table 26 and Table 27 below.

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Table 26: Multi-temperature LoD Precision Study Results

Sample	Dose (ng/mL)	Standard Deviation (ng/mL)		
		Within Run	Between Temperature	Overall SD†
1	0.013	0.0014	0.0018	0.0031
2	0.024	0.0012	0.0000	0.0036
3	0.033	0.0008	0.0000	0.0017
4	0.049	0.0014	0.0024	0.0037
5	0.065	0.0019	0.0038	0.0052

†Overall standard deviation (SD) includes within-run, between-run, and between-temperature variabilities.

Table 27: Multi-temperature LoD Results

Statistic	Calculated LoD (ng/mL)	LoD Upper Boundary (ng/mL)
Limit of Detection across temperatures	0.008	0.009

Multi-Temperature LoD Study Conclusion: The multi-temperature study confirms the results obtained in the standardized study and supports the conclusion that the Limit of Detection for the Access AccuTnI assay is ≤0.030 ng/mL and is unaffected by changes in ambient temperatures across the range of 18°C to 28°C.

8.2.3. Cross-Temperature LoD Analysis

Study Description: The purpose of this analysis was to demonstrate that there is no significant difference in LoD when the assay is used under varying ambient temperature conditions. Statistical analysis was performed using data collected during the standardized LoD studies described above.

Data Analysis: Using the data from the standardized studies (three ambient temperature conditions), within-run, between-run, and between-

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temperature precision were calculated. In this analysis, the between-temperature standard deviation was used to calculate LoD to assess the impact of ambient temperature on LoD. To calculate LoD, each between-temperature standard deviation was multiplied by a constant determined per CLSI EP17-A, and was added to the LoB estimate. To calculate the upper boundary of LoD each between-temperature standard deviation was multiplied by a constant and added to the upper 97.5% confidence limit of LoB.

Acceptance Criteria: Per the AccuTnI Design Inputs, the between-temperature variability for each sample must be less than the precision acceptance criteria (SD ≤0.0084 ng/mL at concentrations ≤0.105 ng/mL). In addition, using between-temperature variability for each sample, the calculated LoD must be ≤0.030 ng/mL.

Results: Results are provided in Table 28 and Table 29 below.

Table 28: Cross-temperature LoD Analysis, Between-Temperature SD

Sample	Dose (ng/mL)	Between-Temperature SD (ng/mL)
1	0.012	0.0019
2	0.022	0.0043
3	0.032	0.0029
4	0.049	0.0027
5	0.065	0.0052

Table 29: Cross-temperature Analysis LoD Results

Statistic	Calculated LoD (ng/mL)	LoD Upper Boundary (ng/mL)
Limit of Detection	0.008	0.010

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Cross-Temperature LoD Analysis Conclusion: The acceptance criteria for this analysis have been met, which demonstrates that the LoD for the AccuTnI assay on the Access 2 instrument is not affected by variations in ambient temperatures between 18°C and 28°C.

8.2.4. Limit of Detection Conclusion

The standardized LoD studies established that LoD is 0.009 ng/mL and meets the acceptance criteria of ≤0.030 ng/mL. The multi-temperature study confirms that LoD is ≤0.030 ng/mL, and the statistical analysis confirms that LoD is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.

8.3. Limit of Quantitation (LoQ)

Limit of Quantitation is the lowest amount of analyte in a sample that can be quantitatively determined with stated acceptable precision and trueness, under stated experimental conditions. Ten laboratory studies were conducted.

Nine standardized studies based on CLSI EP17-A were conducted. Three studies were performed, each at one of three ambient temperature conditions (see Section 8.3.1). The tenth was a confirmation study that was run across six ambient temperatures ranging from 18°C to 28°C (see Section 8.3.2).

Additional statistical analysis was conducted on the pooled data from the standardized study and the multi-temperature study to assess the impact of temperature on the Limit of Quantitation (see Section 8.3.3).

8.3.1. Standardized LoQ Study

Study Description: These studies were performed according to a protocol based on CLSI EP17-A using seven samples with low levels of troponin I. Samples were prepared from a high lithium heparin plasma sample spiked at different levels into a normal lithium heparin plasma pool; resulting

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levels ranged from approximately 0.010 ng/mL to 0.250 ng/mL. Each sample was tested in replicates of three for each run. The study was performed on three instruments using three reagent lots (one reagent pack lot per instrument) at the following ambient temperature conditions:

- 22 runs* at 18 ±2°C
- 22 runs* at 28 ±2°C, and
- 21 runs* at NLC (measured temperatures ranged from 21°C to 25°C)

A single calibration curve was generated for each experiment.

*Per EP17-A, a minimum of 5 runs for a total of 40 replicates per sample are required to establish LoQ.

Data Analysis: Total precision was calculated for each sample. The cTnI concentrations corresponding to a 10% and 20% total CV were determined by interpolation from the precision profile for each determination.

Acceptance Criteria: Per the AccuTnI Design Inputs, the 10% LoQ must be ≤0.06 ng/mL and the 20% LoQ must be ≤0.03 ng/mL.

Results: Results are provided in Table 30 below.

Table 30: Standardized Study LoQ Results

Condition Tested	Instrument	Limit of Quantitation Dose (ng/mL)	
		10% CV	20% CV
LoQ at 18°C	1	0.02	<0.01
	2	0.02	0.01
	3	0.02	<0.01
LoQ at NLC	1	0.03	<0.01
	2	0.02	<0.01
	3	0.02	0.01

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Table 30: Standardized Study LoQ Results

Condition Tested	Instrument	Limit of Quantitation Dose (ng/mL)	
		10% CV	20% CV
LoQ at 28°C	1	0.04	0.02
	2	0.03	0.02
	3	0.03	0.01

Standardized LoQ precision results and profile plots for each experiment are provided in Appendix 26.

Standardized LoQ Study Conclusion: In these nine studies, the LoQ at 10% CV ranged from 0.02 to 0.04 ng/mL and the LoQ at 20% CV ranged from <0.01 to 0.02 ng/mL. These LoQ estimates met the acceptance criteria of ≤0.06 ng/mL and ≤0.03 ng/mL, respectively.

8.3.2. Multi-Temperature Study (Thermal Sensitivity – Impact on LoQ)

Study Description: The purpose of this study is to confirm that change in ambient temperature does not impact the Limit of Quantitation. Seven samples were prepared from a high lithium heparin plasma sample spiked at different levels into a normal lithium heparin plasma pool; resulting levels ranged from approximately 0.010 ng/mL to 0.250 ng/mL. Each sample was tested in replicates of three for each run. A total of 24 runs were completed using three instruments, two reagent lots, and two calibrator lots at the following ambient temperature conditions:

- Four runs at 18 ±2°C
- Four runs at 20 ±2°C
- Four runs at 22 ±2°C
- Four runs at 24 ±2°C
- Four runs at 26 ±2°C
- Four runs at 28 ±2°C.

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A single calibration curve was generated at 24 ±2°C for this study.

Data Analysis: All results at all temperatures were combined for this analysis. The concentrations corresponding to a 10% and 20% total CV (within-run and between-run) were determined by interpolation from the precision profile for each determination. Additionally, between-temperature precision was calculated and compared to the precision acceptance criteria.

Acceptance Criteria: Per the AccuTnI Design Inputs, the 10% LoQ must be ≤0.06 ng/mL and the 20% LoQ must be ≤0.03 ng/mL. Additionally, the between-temperature variability for each sample must be less than the precision acceptance criteria (SD ≤0.0084 ng/mL at concentrations ≤0.105 ng/mL, and the maximum CV must be ≤8% for concentrations >0.105 ng/mL).

Results: Results are provided in Table 31 and Table 32 below.

Table 31: LoQ Multi-temperature Summary

Test Configuration	LoQ (ng/mL)	
	10% CV	20% CV
Instrument 1 / Reagent Pack 1	0.03	<0.01
Instrument 2 / Reagent Pack 2	0.02	<0.01
Instrument 3 / Reagent Pack 3	0.02	<0.01

Table 32: LoQ Summary – Between-temperature Precision

Test Configuration	Max. SD at ≤0.105 ng/mL	Max CV at >0.105 ng/mL
Instrument 1 / Reagent Pack 1	0.0035 ng/mL	3%
Instrument 2 / Reagent Pack 2	0.0047 ng/mL	3%
Instrument 3 / Reagent Pack 3	0.0035 ng/mL	2%

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Multi-temperature LoQ precision results and profile plots for each experiment are provided in Appendix 27.

Multi-Temperature LoQ Study Conclusion: The multi-temperature study confirms the results obtained in the standardized study and supports the conclusion that the 10% LoQ for the Access AccuTnI assay is ≤0.06 ng/mL and the 20% Limit of Quantitation is ≤0.03 ng/mL, and are unaffected by changes in ambient temperatures across the range of 18°C to 28°C.

8.3.3. Cross-Temperature LoQ Analysis

Study Description: The purpose of this analysis was to demonstrate that there is no significant difference in LoQ when the assay is used under varying ambient temperature conditions. Statistical analysis was performed using data collected during the standardized LoQ studies and the multi-temperature studies described above.

Data Analysis: The overall precision values from the multi-temperature study were calculated. Additionally, using overall precision values (within-run, between-run, and between-temperature) from the multi-temperature study, LoQ values at 10% and 20% CV were calculated. The overall precision values from the multi-temperature study were also compared to the precision acceptance criteria. Finally, all data from the nine standardized studies were combined to calculate LoQ values at 10% and 20% CV.

Acceptance Criteria: Per the AccuTnI Design Inputs, the 10% LoQ must be ≤0.06 ng/mL and the 20% LoQ must be ≤0.03 ng/mL. Additionally, the overall variability for each sample must be less than the precision

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acceptance criteria (SD ≤0.0084 ng/mL at concentrations ≤0.105 ng/mL, and the maximum CV must be ≤8% for concentrations >0.105 ng/mL).

Results: Results are provided in Table 33 through Table 35: Cross-temperature LoQ Analysis, Overall Standardized Study Results, and Figure 4 below.

Table 33: Cross-temperature LoQ Analysis based on the Multi-temperature Study

Sample	n	Instrument 1 / Reagent Pack 1			Instrument 2 / Reagent Pack 2			Instrument 3 / Reagent Pack 3		
		Mean Dose (ng/mL)	Overall SD	Overall CV	Mean Dose (ng/mL)	Overall SD	Overall CV	Mean Dose (ng/mL)	Overall SD	Overall CV
1	72	0.010	0.0025	[redacted]	0.011	0.0028	[redacted]	0.010	0.0026	[redacted]
2	72	0.016	0.0040	[redacted]	0.018	0.0041	[redacted]	0.017	0.0036	[redacted]
3	72	0.027	0.0042	[redacted]	0.028	0.0037	[redacted]	0.026	0.0038	[redacted]
4	72	0.048	0.0025	[redacted]	0.049	0.0020	[redacted]	0.047	0.0025	[redacted]
5	72	0.077	0.0055	[redacted]	0.079	0.0055	[redacted]	0.077	0.0039	[redacted]
6	72	0.136	[redacted]	4%	0.139	[redacted]	4%	0.134	[redacted]	3%
7	72	0.267	[redacted]	4%	0.274	[redacted]	3%	0.257	[redacted]	3%

Table 34: Cross-temperature LoQ Analysis, Overall Multi-temperature Study Results

	Instrument 1 / Reagent Pack 1		Instrument 2 / Reagent Pack 2		Instrument 3 / Reagent Pack 3	
%CV	10%	20%	10%	20%	10%	20%
Concentration (ng/mL)	0.04	0.02	0.04	0.02	0.04	0.02

Table 35: Cross-temperature LoQ Analysis, Overall Standardized Study Results

%CV	10%	20%
LoQ Concentration (ng/mL)	0.03	0.01

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

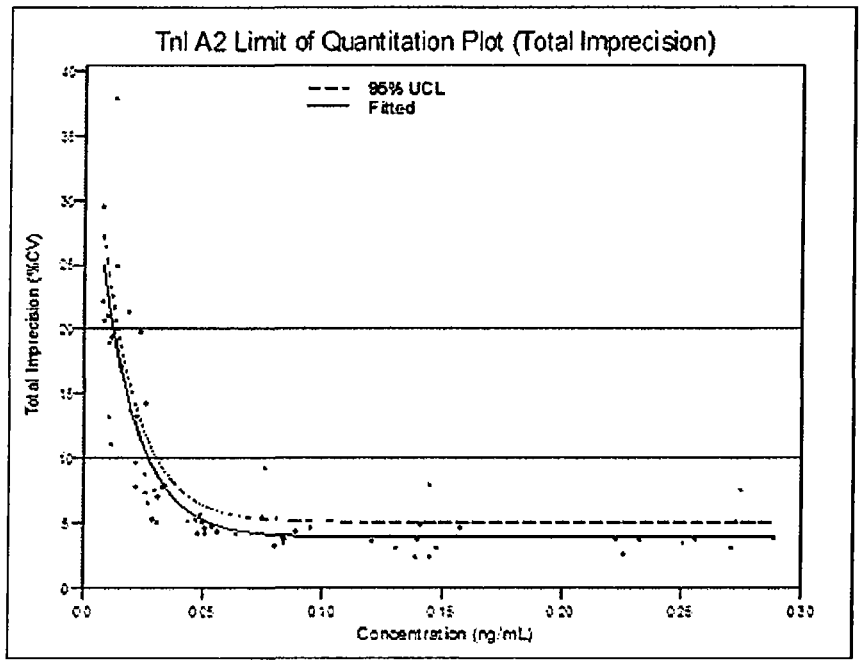

Figure 4: LoQ Overall Limit of Quantitation, From Standardized Studies

Cross-temperature LoQ Analysis Conclusion: Precision estimates calculated from the multi-temperature LoQ study met the precision requirements for overall precision (within-run, between-run, and between-temperature).

LoQ results calculated from the multi-temperature LoQ study using overall precision (within-run, between-run, and between-temperature) met the LoQ acceptance criteria for both the estimates.

The overall LoQ profile created from nine standardized studies met the acceptance criteria for LoQ for 10% and 20% CV values.

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This analysis demonstrates that the LoQ for the AccuTnI assay on the Access 2 instrument is not affected by variations in ambient temperatures between 18°C and 28°C.

8.3.4. Limit of Quantitation Conclusion

The nine standardized LoQ studies established that LoQ at 10% CV ranged from 0.02 to 0.04 ng/mL and the LoQ at 20% CV ranged from 0.01 to 0.02 ng/mL. These LoQ estimates met the acceptance criteria of ≤0.06 ng/mL and ≤0.03 ng/mL respectively. The multi-temperature study confirms that LoQ at 10% CV and 20% CV met the acceptance criteria, and the cross-temperature statistical analysis confirms that LoQ is not affected by changes in ambient temperature across the operating range of 18°C to 28°C.

8.4. Precision

Precision is defined as a measure of closeness of agreement between independent test/measurement results obtained under stipulated conditions. Four laboratory studies were conducted to evaluate precision for the AccuTnI assay on the Access 2 instrument.

Three studies were conducted based on CLSI EP5-A2. Each study was performed at one of three ambient temperature conditions, one of which was conducted at an external site (see Section 8.4.1). The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C (see Section 8.4.2).

Additional statistical analysis was conducted on the data from the multi-temperature study to assess the impact of temperature on overall precision (see Section 8.4.3).

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8.4.1. Standardized Total Precision

Study Description: Three studies based on CLSI EP5-A2 were completed, one at each of three ambient temperature conditions: 18 ±2°C, 28 ±2°C, and NLC (measured temperatures ranged from 20°C to 24°C).

Studies performed at 18 ±2°C and 28 ±2°C were performed internally on one instrument and one reagent pack lot. For both temperature conditions, a total of 42 runs were completed over a 13-day timeframe using three commercial controls, one recombinant cTnI-spiked lithium heparin plasma sample, and one pooled lithium heparin plasma sample. The sample set included one sample <0.08 ng/mL and one sample >50 ng/mL to cover both the assay measuring range and relevant medical decision points. Samples were assayed in replicates of two, two shifts per day, two runs per shift, for a total of 21 shifts. A single calibration curve was generated for each study.

The third study was performed externally at Quest Laboratories, Nichols Institute, Valencia, California under NLC (measured temperatures ranged from 20°C to 24°C). Six commercial controls were run in duplicate, two runs per day for 20 days for a total of 40 runs. The sample set included six samples ranging from 0.02 ng/mL to 15 ng/mL. This study was performed on one reagent lot and one instrument. A single calibration curve was generated for this experiment.

Data Analysis: Total, within-run and between-run precision were calculated for each temperature set point.

Acceptance Criteria: Per the AccuTnI Design Inputs, the standard deviation (SD) must be ≤0.0084 ng/mL for concentrations ≤0.105 ng/mL. For concentrations >0.105 ng/mL, total precision must be ≤8% CV.

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Results: Results are provided in Table 36 through Table 38 below.

Note: In Table 36, Table 37, and Table 38, commercial controls are indicated by "(c)", the recombinant cTnI-spiked lithium heparin sample is indicated by "(s)", and the pooled lithium heparin sample is indicated by "(p)" after the sample number.

Table 36: Total Precision Results, 18°C Temperature Set Point

Sample	n†	Mean Concentration (ng/mL)	Total SD (ng/mL)	Total %CV
1(c)	84	3.405	[redacted]	5
2(p)	84	66.077	[redacted]	3
3(s)	84	0.072	0.0030	[redacted]
4(c)	84	1.072	[redacted]	4
5(c)	84	16.221	[redacted]	5

†Per EP5-A2, a minimum of 40 runs (80 replicates per sample) are required to measure precision.

Table 37: Total Precision, 28°C Temperature Set Point

Sample	n†	Mean Concentration (ng/mL)	Total SD (ng/mL)	Total %CV
1 (c)	84	1.955	[redacted]	5
2 (p)	84	56.361	[redacted]	6
3 (s)	84	0.069	0.0050	[redacted]
4 (c)	84	0.907	[redacted]	5
5 (c)	84	13.966	[redacted]	5

†Per EP5-A2, a minimum of 40 runs (80 replicates per sample) are required to measure precision.

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Table 38: Total Precision, NLC (20°C to 24°C)

Sample	n†	Mean Concentration (ng/mL)	Total SD (ng/mL)	Total %CV
1 (c)	80	0.040	0.0021	[redacted]
2 (c)	80	0.626	[redacted]	3
3 (c)	80	2.580	[redacted]	2
4 (c)	80	0.021	0.0032	[redacted]
5 (c)	80	0.963	[redacted]	3
6 (c)	80	15.001	[redacted]	2

†Per EP5-A2, a minimum of 40 runs (80 replicates per sample) are required to measure precision.

Standardized Total Precision Conclusion: This study showed assay precision met the acceptance criteria for all temperatures tested.

8.4.2. Multi-temperature Study (Thermal Sensitivity – Impact on Precision)

Study Description: The multi-temperature study was conducted over 14 days, and 48 runs were performed at the following ambient temperatures:

- 8 runs at ambient temperature of 18 ±2°C
- 8 runs at ambient temperature of 20 ±2°C
- 8 runs at ambient temperature of 22 ±2°C
- 8 runs at ambient temperature of 24 ±2°C
- 8 runs at ambient temperature of 26 ±2°C
- 8 runs at ambient temperature of 28 ±2°C

A run consisted of two replicates each of five precision samples. One reagent lot on one instrument was used. Three commercial controls, one recombinant cTnI-spiked lithium heparin sample and one pooled lithium heparin sample were used to perform the testing. A single calibration curve was generated at 24 ±2°C for this study.

Data Analysis: Within-run, between-run, total (within-run and between-run) and between-temperature precision were calculated for each sample.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Acceptance Criteria: Per the AccuTnI Design Inputs, the standard deviation (SD) must be ≤0.0084 ng/mL for concentrations ≤0.105 ng/mL. For concentrations >0.105 ng/mL, total precision must be ≤8% CV.

Results: Results are provided in Table 39 below.

Note: Commercial controls are indicated by "(c)", the recombinant cTnI-spiked lithium heparin sample is indicated by "(s)", and the pooled lithium heparin sample is indicated by "(p)" after the sample number.

Table 39: Multi-temperature Study Precision Results

Sample	n	Mean Concentration (ng/mL)	Between-Temperature		Within-Run & Between-Run (Within-Temperature)	
			SD (ng/mL)	%CV	SD (ng/mL)	%CV
1 (s)	96	0.065	0.0014	[redacted]	0.0020	[redacted]
2 (c)	96	0.951	[redacted]	6	[redacted]	6
3 (c)	96	3.274	[redacted]	1	[redacted]	2
4 (c)	94†	14.491	[redacted]	4	[redacted]	3
5 (p)	96	56.599	[redacted]	1	[redacted]	2

†Two data points were lost due to a technician error (wrong sample loaded).

Multi-Temperature Precision Study Conclusion: The multi-temperature study confirms the results found in the standard studies and supports that assay precision (between-temperature, within-run and between-run) across the range of 18°C to 28°C meets the acceptance criteria.

8.4.3. Cross-temperature Precision Analysis

Study Description: The purpose of this analysis was to demonstrate that there is no significant difference in precision when the assay is used under varying ambient temperature conditions. Statistical analysis was

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

performed using data collected during the multi-temperature study described above in Section 8.4.2.

Data Analysis: Using data from the multi-temperature study above, within-run, between-run, and between-temperature precision were calculated for each sample. Overall variability of the five samples was calculated; overall precision included within-run, between-run, and between-temp variability.

Acceptance Criteria: Per the AccuTnI Design Inputs, the SD must be ≤0.0084 ng/mL for concentrations ≤0.105 ng/mL. For concentrations >0.105 ng/mL, precision must be ≤8% CV.

Results: Results are provided in Table 40 below.

Note: Commercial controls are indicated by "(c)," the recombinant cTnI-spiked lithium heparin plasma sample is indicated by "(s)," and the pooled lithium heparin sample is indicated by "(p)" after the sample number.

Table 40: Cross-temperature Precision Analysis Results

Sample	n	Mean Dose (ng/mL)	Overall SD (ng/mL)	Overall %CV
1 (s)	96	0.065	0.0030	[redacted]
2 (c)	96	0.951	[redacted]	8
3 (c)	96	3.274	[redacted]	3
4 (c)	94†	14.491	[redacted]	5
5 (p)	96	56.599	[redacted]	3

† Two data points were lost due to a technician error (wrong sample loaded).

Cross-temperature Precision Analysis Conclusion: This analysis showed that overall precision of the AccuTnI assay is acceptable when the assay is

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used on the Access 2 instrument across multiple ambient temperature conditions.

8.4.4. Precision Conclusion

The standardized precision studies concluded that for total precision, the SD was ≤0.005 ng/mL for concentrations ≤0.105 ng/mL and ≤6% CV for samples >0.105 ng/mL. These results met the acceptance criteria of SD ≤0.0084 ng/mL for concentrations ≤0.105 ng/mL and ≤8% CV for samples >0.105 ng/mL. The multi-temperature study confirmed that total precision met the acceptance criteria, and the cross-temperature statistical analysis confirmed that precision criteria are met at ambient temperatures across the operating range of 18°C to 28°C.

8.5. Linearity

Linearity is defined as the ability (within a given range) to provide results that are directly proportional to the concentration of the analyte in the test sample.

Study Description: Twelve standardized studies based on CLSI EP6-A were conducted to evaluate the linearity of the assay across the reportable range. Four studies were performed, each at one of the following three ambient temperature conditions: 18 ±2°C, 28 ±2°C, and NLC (ranged from 22°C to 24°C). The testing used two lots of reagents on two Access 2 instruments (both lots of reagents were tested on each instrument).

The matrix used for this testing was a synthetic matrix (buffered bovine serum albumin). The high sample tested was the S5 AccuTnI reference calibrator (101 ng/mL). The low sample had a concentration of ≤0.01 ng/mL. In addition to the high and low samples, seven evenly spaced dilutions (Samples 4-10) plus two additional low dilutions (Samples 2 and 3) were created by

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

mixing the high and low samples. Expected concentrations for these samples are provided in Table 41 below.

Table 41: Linearity Sample Concentrations

Sample Number	Expected Concentration (ng/mL)
11	101.0
10	88.4
9	75.8
8	63.1
7	50.5
6	37.9
5	25.3
4	12.6
3	5.1
2	2.0
1	0.01

Data Analysis: A weighted linear regression for each of the tested combinations was calculated and graphed. In addition, 2nd and 3rd order polynomials were fitted to the data to determine coefficients of significance. If a higher order coefficient was significant, the difference between the higher order fit and the linear fit was calculated.

Acceptance Criteria: Per the AccuTnI Design Inputs, the higher order (2nd and 3rd) term of the polynomial fit must be non-significant ($p>0.05$). If it is significant, the fit of the polynomial regression demonstrating significance must have a bias at each sample tested of $\leq 16\%$ for doses >0.105 ng/mL or ≤ 0.0168 ng/mL for doses ≤ 0.105 ng/mL in comparison to the linear regression fit.

Results: Results are provided in Table 42 through Table 44.

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Table 42: Summary of Linearity Results at 18°C

Instrument #	Reagent Lot	18°C Testing		
		p-value <0.05?	Max Bias	Pass/Fail
501007	116677	Yes	10%	Pass
502884	116677	No	[redacted]	Pass
501007	116678	No	[redacted]	Pass
502884	116678	No	[redacted]	Pass

Table 43: Summary of Linearity Results at 28°C

Instrument #	Reagent Lot	28°C Testing		
		p-value <0.05?	Max Bias	Pass/Fail
501007	116677	Yes	-8%	Pass
502884	116677	No	[redacted]	Pass
501007	116678	No	[redacted]	Pass
502884	116678	No	[redacted]	Pass

Table 44: Summary of Linearity Results at NLC

Instrument #	Reagent Lot	NLC Testing		
		p-value <0.05?	Max Bias	Pass/Fail
500616	116677	Yes	5%	Pass
507310	116677	Yes	9%	Pass
500616	116678	No	[redacted]	Pass
507310	116678	Yes	-9%	Pass

Linearity Conclusions:

18 ±2°C Temperature Condition:

Three of four reagent pack and lot-instrument combinations tested at 18°C had non-significant 2nd and 3rd order polynomial coefficient p-values and therefore met the acceptance criteria. Reagent pack 116677 on instrument 501007 showed a significant p-value for the quadratic polynomial fit; however, the maximum bias was <10% and therefore met the acceptance criteria.

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28 ±2°C Temperature Condition:

Three of four reagent pack lot and instrument combinations tested at 28 ±2°C NLC (22-24°C) had non-significant p-values and therefore met the acceptance criteria. Reagent pack 116677 on instrument 501007 showed a significant p-value for the quadratic polynomial fit; however, the maximum bias was -8% and therefore met the acceptance criteria.

Normal Laboratory Conditions (NLC):

One reagent pack lot and instrument combination (reagent pack 116678, instrument 500616,) had non-significant p-values for the higher 2nd and 3rd order polynomial coefficients and therefore met the acceptance criteria. The other three reagent pack lot and instrument combinations showed significant p-values for the quadratic polynomial fit; however, the maximum bias was ±9% and therefore met the acceptance criteria.

Linearity results, including higher order fitted estimates, linearity plots, and difference tables are provided in Appendix 28.

8.5.1. Overall Linearity Conclusion

All reagent pack lot and instrument combinations met the acceptance criteria for linearity at the three ambient temperature conditions tested and demonstrates linearity across the measuring range.

8.6. High Dose Hook Effect

High Dose hook effect can occur when a) the analyte concentration exceeds the capacity of the binding antibody (solid phase) and b) the quantity of the conjugate is not adequate to overwhelm the free analyte while still saturating the solid phase sites causing the resultant value to "hook" back and read on the standard curve, giving a falsely depressed value. The AccuTnI assay was

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

designed to minimize hook effect, and a study was performed to characterize the assay's performance with respect to this phenomenon.

Study Description: This study was performed using six samples exceeding the dose of the AccuTnI S5 calibrator. The samples used were prepared using a purified Troponin complex spiked into a synthetic matrix (buffered bovine serum albumin). Samples were tested in replicates of five using one lot of reagent and one instrument.

Data Analysis: The mean RLU values of the six samples were compared to the RLUs of the AccuTnI S5 calibrator (see Table 45). The RLUs of the samples were plotted graphically (dose vs. RLU) and the data points were visually evaluated for the presence of high dose hook effect (Figure 5).

Acceptance Criteria: Per the AccuTnI Design Inputs, no hook effect from S5 calibrator concentration (approximately 100 ng/mL) up to at least 2,000 ng/mL.

Results: Results are provided in Table 45 and Figure 5 below.

Table 45: Access AccuTnI High Dose Hook Effect Results

Sample	Estimated Dose (ng/mL)	Mean Sample RLU	Access AccuTnI S5 Calibrator RLU
Hook 1	126	38,939,400	19,889,980
Hook 2	506	45,226,860	
Hook 3	1,012	45,709,280	
Hook 4	1,517	45,961,340	
Hook 5	2,023	45,110,860	
Hook 6	2,529	43,484,580	

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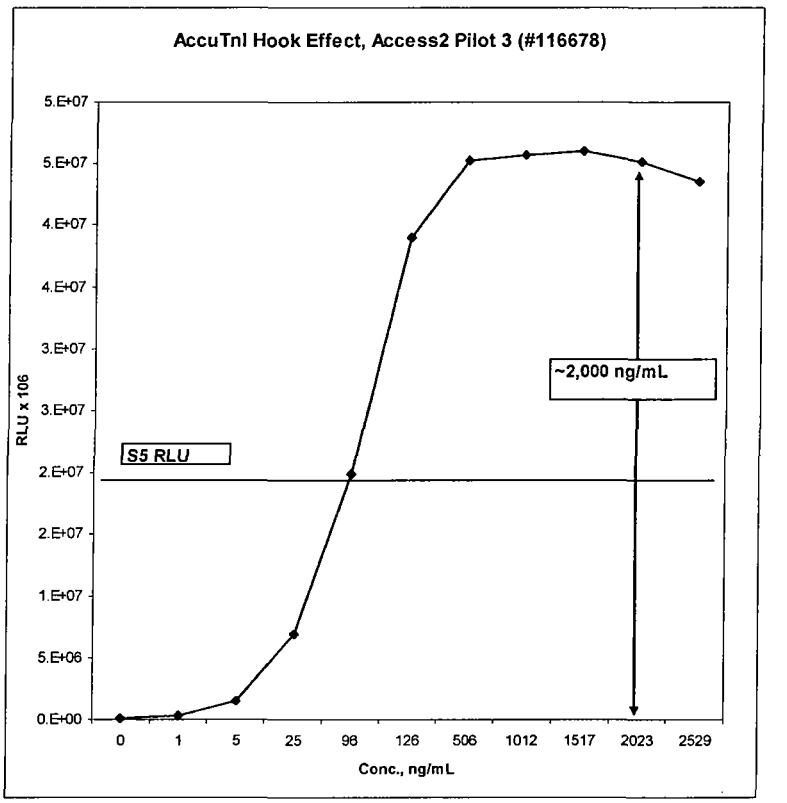

Figure 5: Access AccuTnI Hook Effect

High Dose Hook Effect Conclusion: There is no indication of high dose hook effect from the S5 calibrator concentration to 2,529 ng/mL. The RLUs at 2,529 ng/mL do not fall below the Access AccuTnI S5 calibrator RLU. The acceptance criteria were met.

8.7. Stability

Five studies were conducted to assess the stability of the Access AccuTnI reagent and calibrator materials. The studies, their purpose, and conclusions are presented in the Table 46 below. More detailed summaries on each study are provided in the text following the summary table.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 46: Stability Testing Summary

Study	Purpose	Conclusions	Document Section Below
Reagent Pack Real Time Stability	To determine that length of time when the unopened AccuTnI reagent can produce accurate and reliable results.	At the time of this submission, data for 3 reagent lots met specifications through the six month time point. Stability studies are ongoing.	8.7.1
Reagent Open Pack Stability	To determine that length of time when the opened AccuTnI reagent can produce accurate and reliable results.	The results met the acceptance criteria and indicate the Access AccuTnI reagents on the Access 2 instrument are stable in an open state for 56 days	8.7.2
Stored Calibration Curve Stability	To determine the length of time the stored calibration curve for the AccuTnI assay is stable and produces accurate and reliable results.	The results meet the acceptance criteria and indicate that the Access AccuTnI stored curve on the Access 2 instrument is stable for 56 days.	8.7.3
Calibrator Real Time Stability	To determine that length of time when the unopened AccuTnI calibrators can produce accurate and reliable results.	At the time of this submission, data for three calibrator lots, stored at -20°C, met specifications through at least the four month time point, supporting a shelf life claim of 4 months. Stability studies are ongoing.	8.7.4
Calibrator Open Vial Stability	To determine that length of time when the opened AccuTnI calibrators can produce accurate and reliable results.	At the time of this submission, AccuTnI calibrators are stable at 2° to 10°C for eight days after opening. Stability studies are ongoing.	8.7.5

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8.7.1. Reagent Pack Real Time Stability

Stability of Access AccuTnI was verified on three lots of reagent using two Access 2 instruments at multiple time points.

Study Description: Multiple AccuTnI reagent packs were used to verify the stability of the reagents at the recommended storage conditions (2°C to 10°C). Reagent packs were tested at baseline (time = 0), 3, 4, and 6 month time points. The same three lots were tested at each time point. Test samples included two sets of commercial tri-level controls and three normal patient serum samples. All samples were run in replicates of five on each instrument at each time point. Each time point was run on an unopened pack using a new calibration curve. The study is ongoing and additional time points will include testing up to 13 months in order to achieve the desired 12 month stability claim.

Data Analysis: At each time point the mean value of each control was calculated. From this mean value a "Z" value was calculated as follows:

Z = (Observed dose – Stated dose) / Expected SD

Individual control Z values were averaged to determine the overall mean Z. The difference between this overall mean Z was compared back to the baseline Z to determine the Z from baseline as follows:

Z from baseline = Mean Z at each time point – Mean Z at baseline.

Acceptance Criteria: At each time point:

- All control samples are compared to their stated control values (±2.00 Z from their stated mean).
- Individual controls may be greater than ±2.00 Z from their stated mean as long as that individual control is within ±1.00 Z from baseline.

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- The overall mean Z of control sets cannot be greater than ±1.00 Z from the baseline overall mean Z.
- All replicates of normal patient samples must be ≤0.04 ng/mL on each instrument at each time point

Results: Results are provided in Table 47 through Table 49 below.

Table 47: Reagent Pack Real Time Stability Results, Lot 116676

Time Point	Baseline	3 Months	4 Months	6 Months	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values					**Stated Values (ng/mL)**
Control 1	0.056	0.059	0.062	0.058	0.035-0.079
Control 2	0.798	0.746	0.789	0.738	0.619-0.855
Control 3	3.850	3.656	3.853	3.480	2.961-4.088
Control 4	0.026	0.035	0.031	0.036	0.008-0.052
Control 5	1.086	1.110	1.123	1.032	0.842-1.163
Control 6	15.643	15.694	16.023	14.937	12.402-17.127
Control Mean Z Values					**Specification**
Control 1	-0.09	0.19	0.49	0.11	[redacted]
Control 2	1.03	0.15	0.89	0.02	[redacted]
Control 3	1.16	0.47	1.17	-0.16	[redacted]
Control 4	-0.37	0.47	0.12	0.53	[redacted]
Control 5	1.03	1.33	1.49	0.36	[redacted]
Control 6	0.74	0.79	1.07	0.15	[redacted]
Overall Mean Z	0.58	0.57	0.87	0.17	[redacted]
Z from Baseline	[redacted]	-0.01	0.29	-0.14	±1.00 Z
Pass/Fail	[redacted]	Pass	Pass	Pass	[redacted]
[redacted]					
Individual Assay Normal Patient Results					[redacted]
Patient 0	Pass	Pass	Pass	Pass	All results ≤0.04 ng/mL
Patient 1	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	

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Table 48: Reagent Pack Real Time Stability Results, Lot 116677

Time Point	Baseline	3 Months	4 Months	6 Months	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values					**Stated Values (ng/mL)**
Control 1	0.053	0.059	0.062	0.057	0.035-0.079
Control 2	0.748	0.768	0.78	0.720	0.619-0.855
Control 3	3.646	3.812	3.694	3.275	2.961-4.088
Control 4	0.024	0.035	0.034	0.029	0.008-0.052
Control 5	1.016	1.098	1.090	1.018	0.842-1.163
Control 6	14.669	15.333	15.167	14.217	12.402-17.127
Control Mean Z Values					**Specification**
Control 1	-0.34	0.19	0.45	-0.04	[redacted]
Control 2	0.19	0.53	0.74	-0.30	[redacted]
Control 3	0.43	1.02	0.60	-0.88	[redacted]
Control 4	-0.51	0.44	0.37	-0.07	[redacted]
Control 5	0.16	1.18	1.08	0.19	[redacted]
Control 6	-0.08	0.48	0.34	-0.46	[redacted]
Overall Mean Z	-0.03	0.64	0.60	-0.26	[redacted]
Z from Baseline	[redacted]	0.67	0.63	-0.23	±1.00 Z
Pass/Fail	[redacted]	Pass	Pass	Pass	[redacted]
[redacted]					
Individual Assay Normal Patient Results					[redacted]
Patient 1	Pass	Pass	Pass	Pass	All results ≤0.04 ng/mL
Patient 2	Pass	Pass	Pass	Pass	
Patient 3	Pass	Pass	Pass	Pass	

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Table 49: Reagent Pack Real Time Stability Results, Lot 116678

Time Point	Baseline	3 Month	4 Month	6 Month	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values					Stated Values (ng/mL)
Control 1	0.055	0.058	0.060	0.054	0.035-0.079
Control 2	0.771	0.756	0.758	0.690	0.619-0.855
Control 3	3.750	3.665	3.569	3.304	2.961-4.088
Control 4	0.027	0.031	0.034	0.028	0.008-0.052
Control 5	1.074	1.089	1.072	1.004	0.842-1.163
Control 6	15.599	15.200	15.197	14.614	12.402-17.127
Control Mean Z Values					Specification
Control 1	-0.15	0.11	0.25	-0.32	[redacted]
Control 2	0.58	0.33	0.36	-0.80	[redacted]
Control 3	0.80	0.50	0.16	-0.78	[redacted]
Control 4	-0.31	0.07	0.38	-0.16	[redacted]
Control 5	0.88	1.07	0.86	0.01	[redacted]
Control 6	0.71	0.37	0.37	-0.13	[redacted]
Overall Mean Z	0.42	0.41	0.40	-0.36	[redacted]
Z from Baseline	[redacted]	-0.01	-0.02	-0.78	±1.00 Z
Pass/Fail	[redacted]	Pass	Pass	Pass	[redacted]
[redacted]					
Individual Assay Normal Patient Results					[redacted]
Patient 1	Pass	Pass	Pass	Pass	All results ≤0.04 ng/mL
Patient 2	Pass	Pass	Pass	Pass	
Patient 3	Pass	Pass	Pass	Pass	

Reagent Pack Real Time Stability Conclusion: Stability testing for all lots at all time points tested demonstrated that unopened AccuTnI reagent packs are stable for six months when stored at 2°C to 10°C. Studies are in process to extend this stability to 12 months. This stability extension data will be retained on file at Beckman Coulter.

8.7.2. Reagent Open Pack Stability

Study Description: To verify the fifty-six day stability for the open reagent pack, two commercial controls and two recombinant cTnI-spiked lithium

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heparin plasma samples were tested on day 0 (baseline) after the establishment of a new six-point calibration curve. Opened reagent packs were stored under simulated use conditions at 2°C to 10°C. The study was conducted on one Access 2 instrument and one reagent pack lot. Samples were tested in replicates of four at each time point. Reagent packs were opened on day 0 and tested at 7, 14, 21, 28, 35, 42, 49, 56 and 57 days. At each time point, unopened packs were used to establish a new calibration curve and opened packs were used for testing the samples.

Data Analysis: Mean doses for each sample at each time point were calculated. For samples ≤0.105 ng/mL, doses were scaled according to ±125% of the expected SD (0.0084 ng/mL) to allow all data to be combined for analysis. Mean doses were plotted versus time and compared to baseline values. The best-fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals.

Acceptance Criteria: Per the AccuTnI Design Inputs, open reagent packs must be stable for ≥35 days as determined by a single best fit line through all samples and time points; the fitted line must be within ±10.0% from baseline.

Results: Results are provided in Table 50, Table 51 and Figure 6 below.

Note: values in Table 50 are averages based on all replicates tested at the indicated time point, in ng/mL; commercial controls are indicated by a "(c)" and recombinant cTnI-spiked lithium heparin samples are indicated by a "(s)".

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Table 50: Reagent Open Pack Stability Results, Concentration in ng/mL

Sample	Day									
	0	7	14	21	28	35	42	49	56	57
1 (c)	1.002	0.909	0.956	0.940	0.965	0.949	0.987	0.965	0.955	0.957
2 (c)	14.153	13.435	13.823	13.092	13.715	13.455	13.375	13.761	13.203	13.820
3 (s)†	0.071	0.067	0.069	0.069	0.070	0.072	0.072	0.073	0.074	0.073
4 (s)	41.552	40.126	37.483	41.372	40.887	39.150	43.193	42.690	39.788	42.501

†Note: Sample 3 value is ≤0.105 ng/mL and therefore was scaled as described in the data analysis section above

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Table 51: Reagent Open Pack Stability - Means Compared to Baseline Values

The fitted equation:	96.14 + 0.04603 x Day		
Number of observations used:	40		
The allowed decrease in percentage:	5	10	
The maximum day allowed is:	>56	>56	
Day	35	49	56
Predicted percent change	1.7%	2.4%	2.7%
95% CI band for predicted percent change	[0.5%, 2.9%]	[0.7%, 4.0%]	[0.8%, 4.6%]

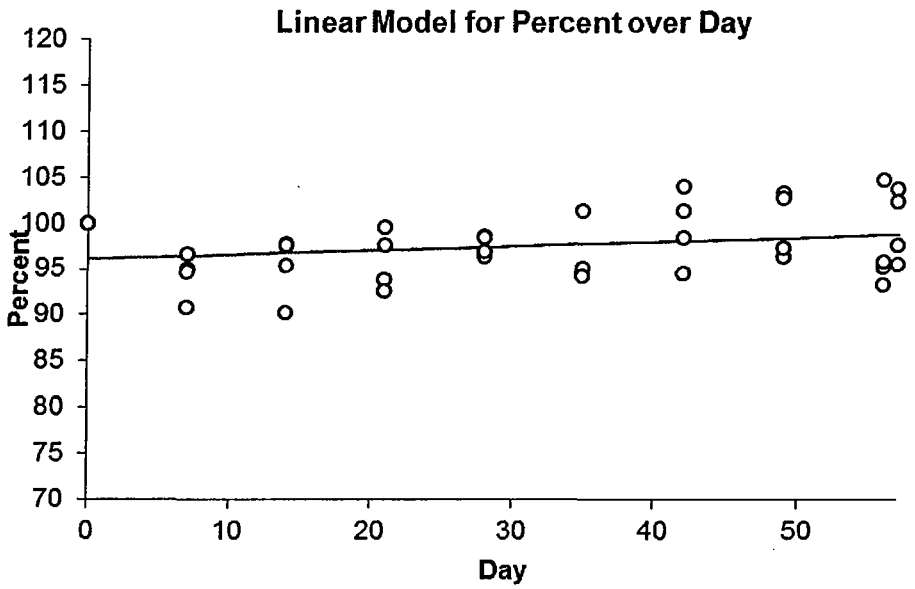

Figure 6: Reagent Open Pack Stability Linear Regression

Reagent Open Pack Stability Conclusion: The results met the acceptance criteria and indicate the Access AccuTnI reagents on the Access 2 instrument are stable in an open state for 56 days.

8.7.3. Stored Calibration Curve Stability

Study Description: To verify the fifty-six day stability of the stored calibration curve, two commercials controls and two recombinant cTnI-

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spiked lithium heparin samples were tested on Day 0 after the establishment of a new six-point calibration curve. The study was run on one Access 2 instrument and one reagent pack lot. Samples were tested in replicates of five at each time point. This study was conducted at 7, 14, 21, 28, 35, 42, 49, 56 and 57 days. At each time point an opened pack was used to establish dose values calculated from the initial stored calibration curve.

Data Analysis: Mean doses for each sample at each time point were calculated. For samples ≤0.105 ng/mL, doses were scaled according to ±125% of the expected SD (0.0084 ng/mL) to allow all data to be combined for analysis. Mean doses were plotted versus time and compared to baseline values. The best-fit linear equation was calculated to estimate the percent dose change with 95% confidence intervals

Acceptance Criteria: Per the AccuTnI Design Inputs, stored calibration curves must be stable for ≥35 days as determined by a single best fit line through all samples and time points; the fitted line must be within ±10.0% from baseline.

Results: Results are provided in Table 52, Table 53, and Figure 7 below.

Note: values in table are averages based on all replicates tested at the indicated time point, in ng/mL; commercial controls are indicated by a "(c)" and recombinant cTnI-spiked lithium heparin samples are indicated by a "(s)" in the table below.

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Table 52: Stored Calibration Curve Stability Results, Concentration in ng/mL

	Day									
Sample	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**57**
1 (c)	1.002	0.950	0.936	0.938	0.961	0.931	0.947	0.979	0.907	0.903
2 (c)	14.153	13.647	13.869	13.394	13.963	13.738	13.823	13.859	13.398	12.871
3 (s)†	0.071	0.071	0.071	0.071	0.071	0.071	0.072	0.073	0.071	0.069
4 (s)	41.552	41.855	35.268	41.517	41.529	41.115	43.116	42.704	40.991	35.026

†Note: Sample 3 value is ≤0.105 ng/mL and therefore was scaled as described in the data analysis section above

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Table 53: Stored Calibration Curve Stability - Means Compared to Baseline			
The fitted equation:	98.88 -0.06336 x Day		
Number of observations used:	40		
The allowed decrease in percentage:	5	10	
The maximum day allowed is:	>56	>56	
Day	35	49	56
Predicted percent change	-2.2%	-3.1%	-3.6%
95% CI band for predicted percent change	[-3.8%, -0.7%]	[-5.2%, -1.1%]	[-6.1%, -1.1%]

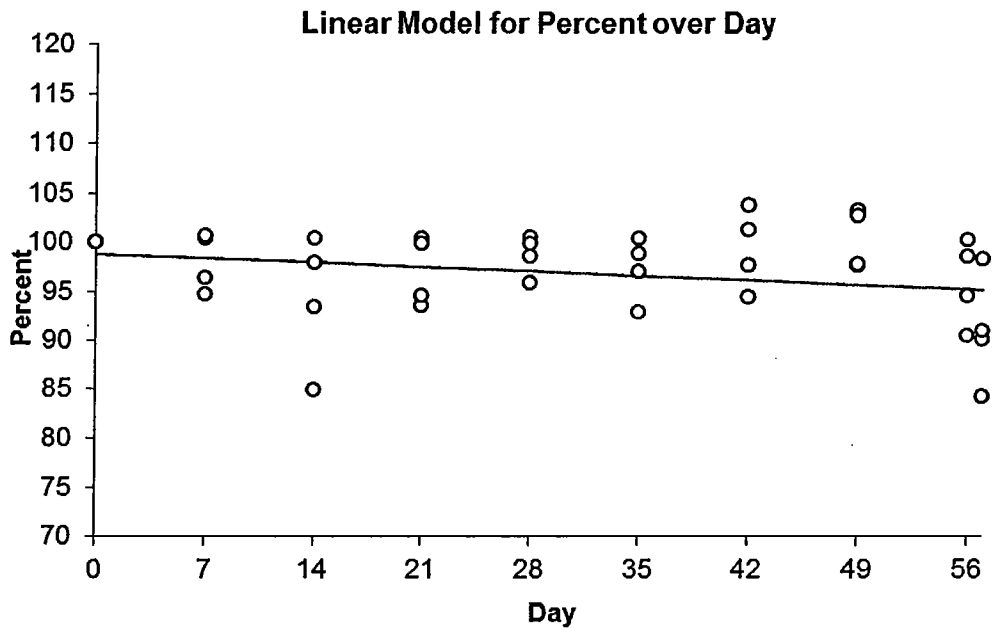

Figure 7: Stored Calibration Curve Stability Linear Regression

Stored Calibration Curve Stability Conclusion: The results meet the acceptance criteria and indicate that the Access AccuTnI stored calibration curve on the Access 2 instrument is stable for 56 days.

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8.7.4. Calibrator Real Time Stability

Stability of Access AccuTnI calibrators was verified on three lots of calibrators using two Access 2 instruments at multiple time points.

Study Description: To verify the stability of the calibrators at the recommended storage conditions (-20°C), multiple AccuTnI calibrator sets were stored at -20°C for real time aging. Three different lots of calibrators were tested. Two lots of calibrators (lots 117302 and 119455) were tested at baseline (time = 0), 2, 3, 4, and 6 month time points. The third lot, 119776, has been tested at baseline, 2 and 4 months to date. Test samples included two sets of commercial tri-level controls (for a total of six), three normal patient serum samples and four levels of primary reference calibrators (S1-S4). Controls and normal patients are run in replicates of five, primary reference calibrator S1 is run in replicates of four and primary reference calibrators S2-S4 are run in replicates of two on each instrument at each test point. The study is ongoing and additional time points will include testing up to 13 months in order to achieve the desired 12 month stability claim.

Data Analysis: At each time point the mean value of each control was calculated. From this mean value a "Z" value was calculated as follows:

Z = (Observed dose – Stated dose) / Expected SD

Individual control Z values were averaged to determine the overall mean Z. The difference between this overall mean Z was compared back to the baseline Z to determine the Z from baseline as follows:

Z from baseline = Mean Z at each time point – Mean Z at baseline.

For primary reference calibrators, the mean dose at each time point is calculated and a percent difference from the baseline mean dose is calculated.

Acceptance Criteria: At each time point:

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- All control samples are compared to their stated control values (±2.00 Z from their stated mean).
- Individual controls may be greater than ±2.00 Z from their stated mean as long as that individual control is within ±1.00 Z from baseline.
- The overall mean Z of control sets cannot be greater than ±1.00 Z from the baseline overall mean.
- For primary reference calibrators, the mean % dose difference from baseline needs to be ±11% for levels S1 and S2, and ±10% for levels S3 and S4.
- All replicates of normal patient samples must be ≤0.04 ng/mL on each instrument at each time point.

Results: Results are provided in Table 54 through Table 56 below.

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Table 54: Calibrator Real Time Stability Results, Lot 117302

Time Point	Baseline	2 Months	3 Months	4 Months	6 Months	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values						**Stated Values (ng/mL)**
Control 1	0.055	0.061	0.055	0.055	0.062	0.035-0.079
Control 2	0.744	0.799	0.763	0.731	0.752	0.619-0.855
Control 3	3.678	3.84	3.541	3.474	3.535	2.961-4.088
Control 4	0.021	0.034	0.025	0.023	0.03	0.008-0.052
Control 5	0.958	1.079	1.062	1.013	1.045	0.842-1.163
Control 6	14.379	15.594	15.832	14.951	14.858	12.402-17.127
Control Mean Z Values						**Specification**
Control 1	-0.18	0.39	-0.18	-0.19	0.46	[redacted]
Control 2	0.12	1.06	0.43	-0.11	0.25	[redacted]
Control 3	0.55	1.12	0.06	-0.18	0.04	[redacted]
Control 4	-0.85	0.39	-0.48	-0.67	0.03	[redacted]
Control 5	-0.56	0.94	0.73	0.12	0.52	[redacted]
Control 6	-0.33	0.7	0.9	0.16	0.08	[redacted]
Overall Mean Z	-0.21	0.77	0.25	-0.14	0.23	[redacted]
Z from Baseline	[redacted]	0.98	0.46	0.07	0.44	±1.00 Z
Individual Assay Normal Patient Results						[redacted]
Patient 0	Pass	Pass	Pass	Pass	Pass	All results ≤0.04 ng/mL
Patient 1	Pass	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	Pass	
Reference Calibrator Mean Dose						[redacted]
Ref S1	0.311	0.316	0.312	0.297	0.327	[redacted]
Ref S2	1.21	1.235	1.231	1.226	1.252	[redacted]
Ref S3	5.01	5.17	5.2	5.14	5.25	[redacted]
Ref S4	24	24.6	25	24.4	25.4	[redacted]
Reference Calibrator % Difference from Baseline						[redacted]
Ref S1	[redacted]	2	0	-5	5	±11%
Ref S2	[redacted]	2	2	1	3	±11%
Ref S3	[redacted]	3	4	3	5	±10%
Ref S4	[redacted]	3	4	2	6	±10%
Pass/Fail	[redacted]	Pass	Pass	Pass	Pass	[redacted]

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Table 55: Calibrator Real Time Stability Results, Lot 117455

Time Point	Baseline	2 Months	3 Months	4 Months	6 Months	
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values						**Stated Values (ng/mL)**
Control 1	0.051	0.055	0.053	0.060	0.059	0.035-0.079
Control 2	0.718	0.773	0.757	0.719	0.735	0.619-0.855
Control 3	3.509	3.744	3.673	3.446	3.342	2.961-4.088
Control 4	0.018	0.025	0.014	0.028	0.026	0.008-0.052
Control 5	0.927	1.058	1.056	0.978	1.017	0.842-1.163
Control 6	13.997	15.543	15.42	14.677	14.896	12.402-17.127
Control Mean Z Values						**Specification**
Control 1	-0.51	-0.22	-0.39	0.24	0.16	[redacted]
Control 2	-0.33	0.61	0.34	-0.3	-0.03	[redacted]
Control 3	-0.05	0.78	0.53	-0.28	-0.64	[redacted]
Control 4	-1.06	-0.44	-1.41	-0.15	-0.35	[redacted]
Control 5	-0.95	0.69	0.66	-0.31	0.17	[redacted]
Control 6	-0.65	0.66	0.56	-0.07	0.11	[redacted]
Overall Mean Z	-0.59	0.35	0.05	-0.14	-0.10	[redacted]
Z from Baseline		0.94	0.64	0.45	0.49	±1.00 Z
Individual Assay Normal Patient Results						
Patient 0	Pass	Pass	Pass	Pass	Pass	All results ≤0.04 ng/mL
Patient 1	Pass	Pass	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	Pass	Pass	
[redacted]						
Reference Calibrator Mean Dose						[redacted]
Ref S1	0.311	0.318	0.305	0.311	0.314	[redacted]
Ref S2	1.195	1.243	1.191	1.184	1.215	[redacted]
Ref S3	4.98	5.2	4.97	5.03	5.04	[redacted]
Ref S4	24.0	25.2	24.5	24.6	24.5	[redacted]
Reference Calibrator % Difference from Baseline						
Ref S1	[redacted]	2	-2	0	1	±11%
Ref S2	[redacted]	4	0	-1	2	±11%
Ref S3	[redacted]	4	0	1	1	±10%
Ref S4	[redacted]	5	2	3	2	±10%
Pass/Fail	[redacted]	Pass	Pass	Pass	Pass	[redacted]

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Table 56: Calibrator Real Time Stability Results, Lot 119776

Time Point	Baseline	2 Months	4 Months	[redacted]
	Mean (ng/mL)	Mean (ng/mL)	Mean (ng/mL)	
Mean Control Values				**Stated Values (ng/mL)**
Control 1	0.055	0.055	0.061	0.035-0.079
Control 2	0.723	0.719	0.755	0.619-0.855
Control 3	3.524	3.41	3.568	2.961-4.088
Control 4	0.033	0.016	0.029	0.008-0.052
Control 5	1.054	0.999	1.036	0.842-1.163
Control 6	14.731	14.765	14.531	12.402-17.127
Control Mean Z Values				**Specification**
Control 1	-0.19	-0.16	0.36	[redacted]
Control 2	-0.24	-0.30	0.30	[redacted]
Control 3	0.00	-0.40	0.16	[redacted]
Control 4	0.32	-1.27	-0.06	[redacted]
Control 5	0.64	-0.05	0.41	[redacted]
Control 6	-0.03	0.00	-0.20	[redacted]
Overall Mean Z	0.08	-0.37	0.16	[redacted]
Z from Baseline	[redacted]	-0.45	0.08	±1.00 Z
Individual Assay Normal Patient Results				[redacted]
Patient 0	Pass	Pass	Pass	All results ≤0.04 ng/mL
Patient 1	Pass	Pass	Pass	
Patient 2	Pass	Pass	Pass	
[redacted]				[redacted]
Reference Calibrator Mean Dose				[redacted]
Ref S1	0.317	0.319	0.324	[redacted]
Ref S2	1.201	1.229	1.202	[redacted]
Ref S3	5.00	5.10	5.05	[redacted]
Ref S4	23.6	24.0	24.4	[redacted]
Reference Calibrator % Difference from Baseline				[redacted]
Ref S1	[redacted]	1	2	±11%
Ref S2	[redacted]	2	0	±11%
Ref S3	[redacted]	2	1	±10%
Ref S4	[redacted]	2	3	±10%
Pass/Fail	[redacted]	Pass	Pass	[redacted]

Calibrator Real Time Stability Conclusion: The results met the acceptance criteria and indicate the Access AccuTnI Calibrators are stable at -20°C for 4

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

months, based on the shortest amount of testing available to date (lot 119776). Studies are in process to extend this stability to 12 months. This stability extension data will be retained on file at Beckman Coulter

8.7.5. Calibrator Open Vial Stability

Calibrator open vial stability is defined as the amount of time that AccuTnI calibrators are stable at 2°C to 10°C after the material has been thawed and opened. The long-term storage conditions for the AccuTnI calibrators is -20°C or colder.

Study Description: The baseline was generated by running two unopened calibration curves over two days on one Access 2 instrument and one reagent pack lot. Four levels of commercial controls were tested in replicates of three on each day. Multiple calibrator sets were thawed on day 0, opened, and then stored at 2°C to 10°C for subsequent testing. At each subsequent time point, the last being >60 days, one set of calibrators that was opened on Day 0 and stored at 2°C to 10°C was run as a calibration curve.

Data Analysis: The baseline values were established by averaging the results from the two days of baseline testing for each of the four controls. Mean doses for each sample at each time point were calculated.

Note: For the interim analysis listed below (since this is an ongoing stability study), a percent-difference from baseline was calculated for each control and had to meet the ±10% specification. In addition to the percent-difference, controls with predetermined ranges were run as assay validity controls and were used as a criteria for accepting to accept the time point. This alternate analysis was used since a linear regression cannot be performed on a single time point.

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When more data are available, for samples ≤0.105 ng/mL, doses will be scaled according to ±125% of the expected SD (0.0084 ng/mL) to allow all data to be combined for analysis. Mean doses will be plotted versus time and compared to baseline values. The best-fit linear equation will be calculated to estimate the percent dose change with 95% confidence intervals

Acceptance Criteria: Per the AccuTnI Design Inputs, open calibrator vials must be stable for ≥60 days as determined by a single best fit line through all samples and time points; the fitted line must be within ±10.0% from baseline.

Results: Results are provided in Table 57 and Table 58 below.

Table 57: Calibrator Open Vial Stability Results, % Difference, Day 8

Sample	Mean (ng/mL)		% Difference
	Day 0	Day 8	
Control 1	0.055	0.055	-0.4%
Control 2	0.575	0.585	1.7%
Control 3	1.831	1.834	0.1%
Control 4	12.887	13.750	6.7%
		Overall Mean % Difference:	2.1%

Table 58: Assay Validity Control Data for Day 8 Testing

Validity Control Sample	Mean Dose (ng/mL)	Stated Values (ng/mL)	Status
Validity Control 1	0.023	0.008-0.052	Pass
Validity Control 2	0.890	0.842-1.163	Pass
Validity Control 3	13.358	12.402-17.127	Pass

Calibrator Open Vial Stability Conclusion: Current data indicates that AccuTnI calibrators are stable at 2°C to 10°C for eight days. Studies are in process to extend this stability to 60 days. This stability extension data will be retained on file at Beckman Coulter. A linear regression, per the acceptance criteria, will be performed on the final data.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

8.8. Interference and Analytical Specificity

Interference is defined as a cause of clinically significant bias in the measured analyte concentration due to the effect of another component or property of the sample. Analytical Specificity is defined as the ability of a measurement procedure to measure solely the measurand. Potential interfering substances were tested using the Access AccuTnI assay on one lot of reagent using six Access 2 instruments.

Study Description: Three studies based on CLSI EP7-A2 were completed, one at each of three ambient temperature conditions: 18 ±2°C, 28 ±2°C, and NLC (ranged from 21.8°C to 25.3°C).

Potential endogenous interferents (bilirubin, fibrinogen, triglycerides, hemoglobin, human serum albumin), exogenous interferents (e.g. acetylsalicylic acid, acetaminophen, ibuprofen), and drug interferents were evaluated. Two levels of each interferent were added to lithium heparin plasma pools at two clinically relevant concentrations of cTnI (one normal containing ≤0.01 ng/mL, and one elevated containing approximately 0.5 ng/mL).

Stock solutions of potential interferents were prepared gravimetrically using an appropriate solvent, and this stock solution was added directly to the lithium heparin plasma sample in no more than 5% (v/v) final concentration. Control samples were prepared in the same manner using the matched solvent, without the interferent added. Control and test samples were tested on an Access 2 instrument within 3.5 hours of preparation.

cTnI-containing samples were tested in replicates of five to allow detection of any difference between the test and the diluent-spiked control of >10%. Normal lithium heparin plasma samples were tested in replicates of ten to detect a difference of >0.01 ng/mL. All substances were tested at all three temperature conditions.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

For any substance found to interfere >10% at the original test levels, a dose-response dilution series was performed by mixing the high interferent level with the low interferent level to make three intermediate dilutions. This dilution series was tested at all three temperature conditions to determine the point at which the interferent showed acceptable results across all temperatures.

Data Analysis: For each substance tested with the analyte-containing sample, the troponin I concentration (ng/mL) obtained in the spiked sample was compared to the concentration (ng/mL) obtained with the control sample and applied in the following formula:

% Interference = [(mean dose of interferent-spiked sample - mean dose of diluent-spiked sample) / Mean dose of diluent-spiked sample] x 100

For any substance tested with the normal sample, the cTnI concentration (ng/mL) obtained in the spiked sample was compared to the acceptance criteria (less than or equal to established 99th percentile Upper Reference Limit or "URL"). No interference above the established 99th percentile URL was observed; therefore a difference between test and control per the acceptance criteria was not calculated.

Acceptance Criteria: This study is intended to characterize any interference with specific substances. Per the AccuTnI Design Inputs:

- For doses >0.105 ng/mL, the percent change must be ≤10.0% from the diluent control
- For normal samples, either the test sample must read less than or equal to the established 99th percentile URL; or, if the test samples exceed the established 99th percentile URL, the difference between the test and the control sample must be ≤0.01 ng/mL

Results: Results are provided in Table 59 and Table 60 below.

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Table 59: Interfering Substances Results

Substance Name	Concentration Added	Dose (ng/mL) cTnI Conc 1 (normal)			% Interference cTnI Conc 2 (~0.5 ng/mL)		
		18°C	NLC	28°C	18°C	NLC	28°C
Acetaminophen	3 mg/dL	0.00	0.00	0.00	2.7	-2.8	-1.9
	20 mg/dL	0.00	0.00	0.00	1.8	0.0	-8.8
Acetylsalicylic Acid	50 mg/dL	0.00	0.00	0.00	-6.3	-2.7	-4.4
	65 mg/dL	0.00	0.00	0.00	-0.4	2.0	-6.3
Allopurinol	2 mg/dL	0.00	0.00	0.00	5.6	1.2	-3.8
	40 mg/dL	0.00	0.01	0.00	-2.9	-3.6	-0.1
Ambroxol	8.6 mg/dL	0.00	0.00	0.00	0.9	-0.5	0.1
	40 mg/dL	0.00	0.00	0.00	-0.6	0.6	-1.3
Ampicillin	1.8 mg/dL	0.00	0.00	0.00	-0.3	-4.9	-2.6
	5 mg/dL	0.00	0.00	0.00	-0.6	2.7	0.0
Ascorbic Acid	4 mg/dL	0.00	0.00	0.00	-3.2	-2.5	0.1
	6 mg/dL	0.00	0.00	0.00	1.7	0.7	3.9
Atenolol	0.2 mg/dL	0.00	0.00	0.00	-1.0	-0.6	-1.9
	1 mg/dL	0.00	0.00	0.00	-2.1	0.3	-4.7
Bilirubin (conj.)	5 mg/dL	0.00	0.00	0.00	-2.5	-10.0	-4.8
	40 mg/dL	0.00	0.00	0.00	-4.7	3.6	-8.9
Bilirubin (unconj.)	4 mg/dL	0.00	0.00	0.00	9.0	-4.4	0.7
	40 mg/dL	0.00	0.00	0.00	-5.4	-5.3	-9.6
Biotin	10 ng/mL	0.00	0.00	0.00	4.9	0.0	6.5
	290 ng/mL	0.00	0.00	0.00	-1.0	-0.4	4.8
Caffeine	2 mg/dL	0.00	0.00	0.00	0.6	-1.8	-2.0
	10 mg/dL	0.00	0.00	0.00	0.6	3.8	-0.4
Captopril	0.5 mg/dL	0.00	0.00	0.00	-5.2	-3.5	-2.3
	5 mg/dL	0.00	0.00	0.00	-3.9	-9.4	0.1
Cinnarizine	4.8 mg/dL	0.00	0.00	0.01	-2.7	-0.9	-7.3
	40 mg/dL	0.00	0.00	0.01	-1.7	-1.5	1.6
Cocaine	1 mg/dL	0.00	0.00	0.00	-3.6	-2.0	-9.1
	2 mg/dL	0.00	0.00	0.00	-1.3	-1.0	-5.7
Diclofenac	2 mg/dL	0.00	0.00	0.00	-2.7	1.2	-2.6
	5 mg/dL	0.00	0.00	0.00	-0.2	-1.3	3.4
Digoxin	2 ng/mL	0.00	0.00	0.00	-0.3	-0.8	-0.6
	200 ng/mL	0.00	0.00	0.01	2.2	-0.3	-6.5
Dopamine	30 mg/dL	0.00	0.00	0.00	See Table 60 below		
	65 mg/dL	0.00	0.00	0.00			
Erythromycin	2 mg/dL	0.01	0.01	0.00	-1.0	0.3	-3.4
	20 mg/dL	0.01	0.01	0.00	5.7	5.7	2.1
Fibrinogen	100 mg/dL	0.00	0.00	0.00	-3.8	1.1	7.7
	1000 mg/dL	0.00	0.00	0.00	-5.2	-5.0	1.0
Furosemide	2 mg/dL	0.00	0.00	0.00	-4.0	2.3	-2.9
	3 mg/dL	0.00	0.00	0.00	-3.9	0.9	3.2
Hemoglobin	2 mg/mL	0.00	0.00	0.00	-2.9	-3.6	1.8
	5 mg/mL	0.00	0.01	0.00	-8.7	-8.5	-6.2
Human Serum Albumin	5000 mg/dL	0.00	0.00	0.00	-5.5	0.1	4.2
	6000 mg/dL	0.00	0.00	0.00	-3.8	-3.4	-2.5
Ibuprofen	40 mg/dL	0.00	0.00	0.00	-1.2	0.4	-0.5
	50 mg/dL	0.00	0.00	0.00	4.0	0.2	-2.3
Low MW Heparin	5 µg/mL	0.00	0.00	0.01	-4.1	-3.1	0.8
	71 µg/mL	0.00	0.00	0.01	1.7	9.0	-0.4

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Table 59: Interfering Substances Results

Substance Name	Concentration Added	Dose (ng/mL) cTnI Conc 1 (normal)			% Interference cTnI Conc 2 (~0.5 ng/mL)		
		18°C	NLC	28°C	18°C	NLC	28°C
Methyldopa	0.75 mg/dL	0.00	0.00	0.00	8.3	-5.3	0.4
	2.5 mg/dL	0.01	0.00	0.00	7.3	3.1	2.1
Nifedipine	20 µg/dL	0.00	0.01	0.00	-0.9	-0.2	-1.8
	60 µg /dL	0.00	0.00	0.00	5.1	0.3	-0.7
Nitrofurantoin	0.2 mg/dL	0.00	0.00	0.00	-0.7	7.3	-1.8
	6.4 mg/dL	0.00	0.00	0.00	0.8	4.5	-1.7
Nystatin	0.7 mg/dL	0.00	0.00	0.00	8.7	-1.6	-0.3
	2.15 mg/dL	0.00	0.00	0.00	1.6	-0.4	1.4
Oxytetracycline	0.5 mg/dL	0.00	0.00	0.00	-2.9	-1.0	1.5
	24 mg/dL	0.00	0.00	0.00	-0.9	0.3	2.5
Phenytoin	5 mg/dL	0.00	0.00	0.00	-0.9	-5.2	1.6
	10 mg/dL	0.00	0.00	0.00	-4.1	3.6	-0.4
Propranolol	1 µg/mL	0.00	0.00	0.00	-1.0	-0.6	0.5
	500 µg/mL	0.00	0.00	0.00	0.8	-0.2	1.7
Quinidine	0.6 mg/dL	0.00	0.00	0.00	0.6	-5.2	-2.3
	2 mg/dL	0.00	0.00	0.00	0.5	0.1	0.2
Simvastatin	4 ug/mL	0.00	0.00	0.00	-2.1	-1.2	0.7
	200 ug/mL	0.00	0.00	0.00	0.5	-2.4	0.7
Sodium Heparin	8 U/mL	0.00	0.00	0.01	-1.2	5.5	-3.3
	28.8 U/mL	0.00	0.00	0.00	-2.5	-2.1	-0.3
Theophylline	2 mg/dL	0.00	0.00	0.00	9.2	-1.3	1.1
	25 mg/dL	0.01	0.01	0.00	-2.6	-1.8	-0.9
Triglycerides	1 mg/dL	0.00	0.00	0.00	-3.2	-0.5	-3.0
	500 mg/dL	0.00	0.00	0.00	-1.1	-5.7	-2.8
Trimethoprim	1.8 mg/dL	0.00	0.00	0.00	-2.3	-2.0	-1.5
	7.5 mg/dL	0.00	0.00	0.00	-3.3	-2.9	0.0
Verapamil	0.1 mg/dL	0.00	0.00	0.00	0.3	1.6	2.0
	16 mg/dL	0.00	0.00	0.00	0.5	2.9	0.3
Warfarin	3 ug/mL	0.00	0.00	0.00	2.3	-2.4	1.7
	30 ug/mL	0.00	0.00	0.00	7.3	0.6	6.4

Table 60: Dopamine Dilution Series

Substance Name	Concentration Added	% Interference cTnI Conc 2 (~0.5 ng/mL)		
		18C	NLC	28C
Dopamine	16.25 mg/dL	3.3	4.3	8.9
	32.5 mg/dL	4.8	3.9	9.4
	48.75 mg/dL	6.2	3.5	9.8
	65.0 mg/dL	8.3	8.1	14.2

Interference and Analytical Specificity Conclusion: No compound demonstrated interference with normal (<0.01 ng/mL) samples at the three temperatures tested.

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For cTnI-containing (0.5 ng/mL) samples, all but one tested compound were within 10.0% of their respective controls at three temperatures, and therefore demonstrate less than 10.0% interference. One compound, Dopamine, demonstrated 14.2% interference at 65 mg/dL. Per CLSI EP7-A2, this interferent was further diluted and retested at all temperatures. At concentrations of 48.75 mg/dL and less, dopamine demonstrates less than 10.0% interference. This information is included in the product insert.

8.9. Cross-reactivity

Cross-reactivity is defined as a measure of the specificity of an immunochemical method whereby a molecule structurally similar to an antigen may interfere with the antibody. Potential cross-reactivity in Access AccuTnI assay was tested on one lot of reagents across six Access 2 instruments.

Study Description: Three studies based on CLSI EP7-A2 were completed, one at each of three ambient temperature conditions: 18 ±2°C, 28 ±2°C, and NLC (ranged from 21.8°C to 25.3°C).

Potential cross-reactive substances were added to lithium heparin plasma pools at two concentrations of cTnI (one normal containing ≤0.01 ng/mL and one containing approximately 0.5 ng/mL). Stock solutions of potential cross-reactants were prepared gravimetrically using an appropriate solvent, and this stock solution was added directly to the lithium heparin plasma sample in no more than 5% (v/v) final concentration. Control samples were prepared in the same manner using the matched solvent, without the cross-reactant added. Control and test samples were tested on an Access 2 instrument within 3.5 hours of preparation. All potential cross-reactants were tested at all three temperature conditions.

Data Analysis: For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration (ng/mL) obtained with the control sample and applied in the following formula:

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% cross-reactivity = [(mean dose of cross-reactant spiked matrix - mean dose of diluent-spiked control matrix) / amount (ng/mL) of cross-reactant spiked] x 100

Acceptance Criteria: This study is intended to characterize any cross-reactivity with specific substances. Per the AccuTnI Design Inputs, the percent cross reactivity must be ≤1.00%.

Results: Results are provided in Table 61 below.

Table 61: Cross-Reactivity Results

Substance Added	Concentration Added (ng/mL)	% Cross-Reactivity cTnI Conc 1 (normal)			% Cross-Reactivity cTnI Conc 2 (~0.5 ng/mL)		
		18°C	NLC	28°C	18°C	NLC	28°C
Actin	1000	0.00	0.00	0.00	0.00	0.00	0.00
Cardiac troponin C	1000	0.00	0.00	0.00	0.00	0.00	0.00
Cardiac troponin T	1000	0.01	0.01	0.01	0.00	0.00	0.00
Human CKMB	1000	0.10	0.07	0.06	0.11	0.08	0.06
Myoglobin	1000	0.00	0.00	0.00	0.00	0.00	0.00
Myosin	1000	0.00	0.00	0.00	0.00	0.00	0.00
Skeletal troponin I	1000	0.00	0.00	0.00	0.00	0.00	0.00
Tropomyosin	1000	0.00	0.00	0.00	0.00	0.00	0.00

Cross-reactivity Conclusion: All cTnI values observed in the presence of each substance demonstrated less than 1.00% cross-reactivity.

8.10. Sample Matrix Comparison

Study Description: This study was performed three times, once at each of three ambient temperature conditions: 18 ±2°C, 23 ±2°C and 28 ±2°C on two Access 2 instruments using one reagent pack lot. The study included 103 matched serum and lithium heparin plasma samples spanning the range of 0.006 to 77.961 ng/mL which were run in duplicate at each temperature condition. No spiked or diluted samples were used in this study.

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Data Analysis: Duplicate results for each sample run at each temperature set point were averaged to determine the best estimate. A Passing-Bablok method comparison was performed on the best estimates to calculate the correlation between the sample types at each temperature set point.

Acceptance Criteria: Per the AccuTnI Design Inputs, Passing-Bablok Slope must be 1.00 ±0.10; r >0.95.

Results: Results are provided in Table 62 and Figure 8 through Figure 10 below.

Table 62: Lithium Heparin Plasma vs. Serum Comparison

Temperature	Dose Range (ng/mL)		Slope	95% CI		r-value	n
	Low	High		Lower	Upper		
18°C	0.006	77.961	**1.03**	1.02	1.06	**0.99**	103
23°C	0.007	71.841	**1.02**	0.99	1.04	**0.99**	103
28°C	0.006	66.761	**1.04**	1.01	1.06	**0.99**	103

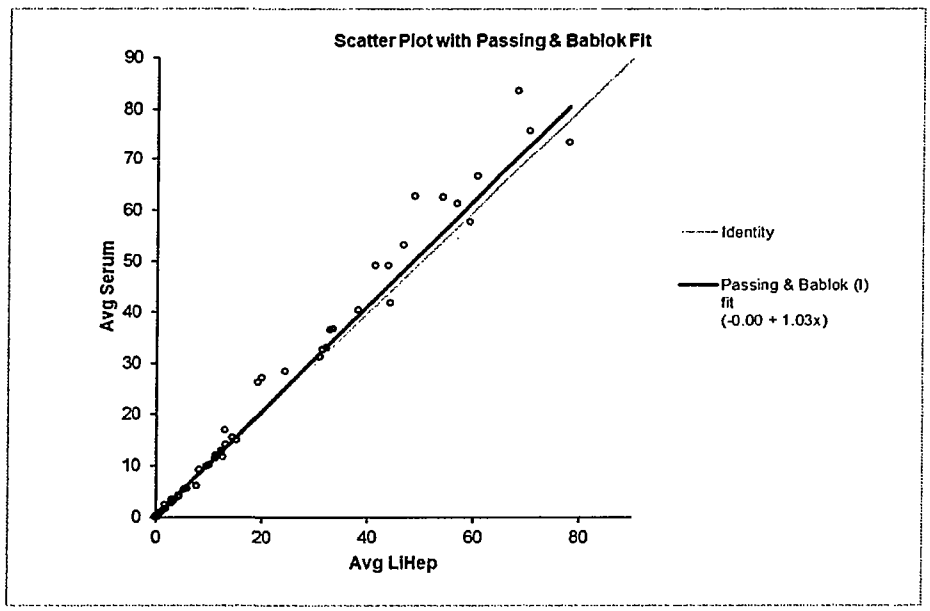

Figure 8: Passing-Bablok Plot, 18°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL

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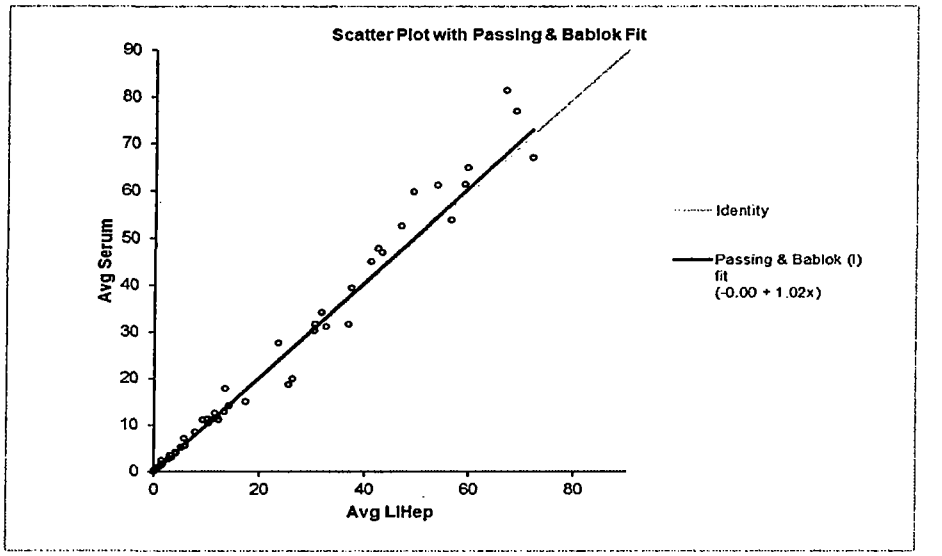

Figure 9: Passing-Bablok Plot, 23°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL

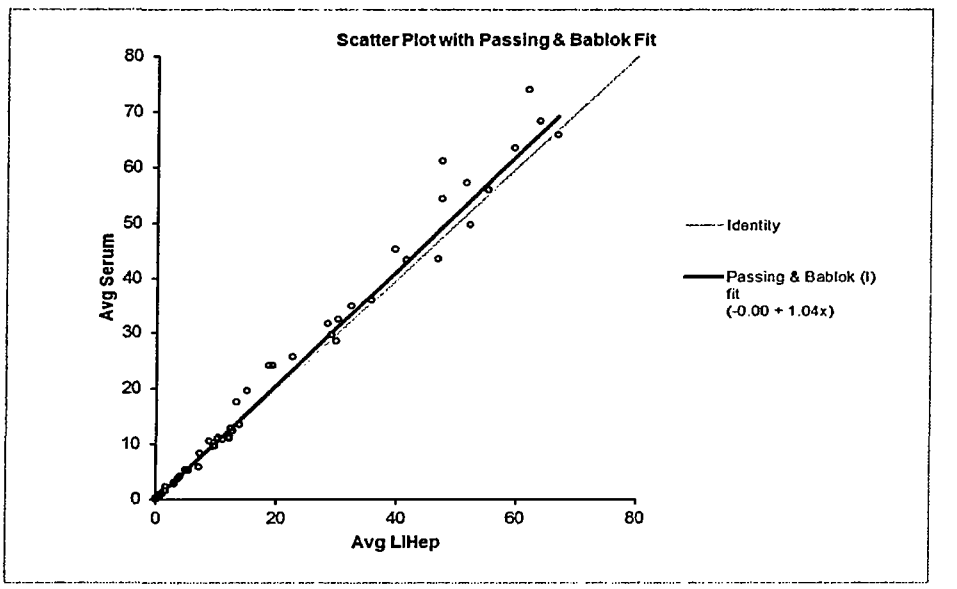

Figure 10: Passing-Bablok Plot, 28°C, Lithium Heparin Plasma vs. Serum, concentrations in ng/mL

Sample Matrix Comparison Conclusion: Results from matched lithium heparin plasma and serum samples are comparable, and acceptance criteria were met. Both sample types are acceptable for use with the AccuTnI assay on the Access 2 instrument.

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8.11. HAMA / Heterophile

Testing of characterized human anti-mouse antibody (HAMA) / heterophile samples was done to evaluate blocker effectiveness in the AccuTnI assay. Testing was done on one lot of reagent using one Access 2 instrument.

Study Description: Testing was performed on a "Control" reagent pack with the conjugate formulation containing blockers and a "Test" reagent pack where the conjugate formulation did not contain blockers. The same lot of stock conjugate was used for each reagent pack. All other reagent components (paramagnetic particles, ancillary buffer, and NaOH) were matched for the control and test packs. The 45 suspected HAMA or heterophile samples used for this testing were either qualified internally using a generic heterophilic screening assay, or were characterized by vendors as a specific type of interferent sample. Samples were tested in triplicate on each reagent pack (control and test). Testing was performed on one Access 2 instrument.

Data Analysis: Relative light unit (RLU) output and doses were compared for the suspected HAMA/heterophile interferent samples from both the test and control pack.

"True interference" was defined as: when the percent difference of RLUs between the control and the test pack is greater than the %CV obtained for the replicates of the control pack.

Samples were sorted into three categories of analysis:

- *Insignificant*: 0-15% RLU suppression between test and control pack
- *Moderate*: 15-50% RLU suppression between test and control pack
- *Highly reactive*: >50% RLU suppression between test and control pack

Acceptance Criteria: This study is intended to characterize blocker effectiveness.

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Results:

Percentage of samples exhibiting "true interference":

- 93% (42/45) of the samples exhibited "true interference".
- 7% (3/45) of the samples evaluated did not demonstrate any true interference

Degree of Reactivity:

- 38% (16/42) of the true interferent samples showed an insignificant difference (0-15%) between the test pack and control pack
- 33% (14/42) of the true interferent samples were moderately reactive (15-50%) and the signals were effectively suppressed by the blocking reagents
- 29% (12/42) of the true interferent samples were very highly reactive (>50%) and were effectively suppressed by the blocking reagents

HAMA / Heterophile Conclusion: The AccuTnI reagent pack has been formulated to minimize the effects of HAMA and Heterophile interference.

Immunoenzymatic assay technology may demonstrate interferences from heterophile antibodies, including HAMA. While this assay has been formulated to minimize the effects of these antibodies, the following cautionary note has been included in the "Limitations of the Procedure" section of the product insert.

> "For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g., HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

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8.12. Thermal Sensitivity – Robustness

For purposes of this study, robustness is defined as a measure of the assay's capacity to remain unaffected by small but deliberate variations in ambient temperature and provides an indication of reliability during normal usage.

Study Description: The purpose of this study was to assess the effect of ambient temperatures on AccuTnI assay performance. The study incorporated multiple sample types (native plasma/serum, spiked plasma/serum, and quality control materials), ten levels of troponin I, two instruments, and six ambient temperature conditions:

- One run at 16°C ±1°C
- One run at 19°C ±1°C
- One run at 22°C ±1°C
- One run at 25°C ±1°C
- One run at 27°C ±1°C
- One run at 30°C ±1°C

This temperature range was specifically chosen to exceed the recommended temperature range of 18°C to 28°C.

Each sample was tested in replicates of five on each instrument and at each ambient temperature condition. A calibration curve was established at each temperature condition on each instrument.

Data Analysis: Individual sample results were calculated from the calibration curve established at each temperature (*i.e.,* five replicates generated at 18°C were calculated from the calibration curves at each of six temperatures for a total of 30 results). A percent difference in the average dose at each temperature compared to the mean dose achieved at 25°C ambient temperature was calculated for each sample and plotted as a function of temperature. The analysis was performed for each individual instrument and both instruments combined.

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Acceptance Criteria: Per the AccuTnI Design Inputs, the slope term of the linear fit across all samples is either 1) non-significant ($p>0.05$) or 2) significant, but has an average slope ≤ 0.010 ($\leq 1\%$ per degree Celsius).

Results: Results are provided in Table 63 below.

Table 63: Thermal Sensitivity/Robustness Results

Analysis	p-value	Slope
Instrument 1	<0.0001	-0.007
Instrument 2	<0.0001	-0.003
Combined Instruments	<0.0001	-0.005

Thermal Sensitivity - Robustness Conclusion: This study met acceptance criteria. The slope term of the linear fit is significant ($p<0.05$) but is ≤ 0.010 for all three analyses, indicating less than a 1% per degree temperature effect.

8.13. Thermal Sensitivity – Impact on Low Dose Concordance/Agreement

Study Description: This study was performed to demonstrate the impact of ambient temperature differences on concordance (agreement) of low dose samples. Two-hundred twenty (220) lithium heparin plasma samples near the clinical cutoff were tested using two reagent pack lots on two Access 2 instruments at six ambient temperature conditions: 18, 20, 22, 24, 26 and 28°C. Each sample was divided into three aliquots, and tested at three of these temperatures: either 18, 22 and 26 °C, or 20, 24 and 28°C±2 °C. See Table 64 for the details of study design. At each temperature, each sample aliquot was run in replicates of two.

Table 64: Study Design for Concordance/Agreement Testing

Test Set	Aliquot #	Reagent Pack and Instrument #	Temperature (±2°C)
Samples 1-55	1	1	18
Samples 56-110	1	2	18
Samples 111-166	1	1	20

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 64: Study Design for Concordance/Agreement Testing

Test Set	Aliquot #	Reagent Pack and Instrument #	Temperature (±2°C)
Samples 167-220	1	2	20
Samples 1-55	2	1	22
Samples 56-110	2	2	22
Samples 111-166	2	1	24
Samples 167-220	2	2	24
Samples 1-55	3	1	26
Samples 56-110	3	2	26
Samples 111-166	3	1	28
Samples 167-220	3	2	28

Data Analysis: For each sample, three concentration comparisons were made between its three temperatures. A 2 x 2 table was created for comparisons, where a sample's measured concentration at a lower temperature was compared to that same sample's concentration at a higher temperature. The analysis enumerated the result categories as being below or above the cutoff. Two cutoffs were evaluated:

- 0.02 ng/mL (the 99th percentile Upper Reference Limit or URL)
- 0.03 ng/mL (the clinical Acute Myocardial Infarction or AMI cutoff)

A McNemar analysis was performed to determine whether the number of mismatched comparisons was due to random scatter or a systematic difference. For this analysis, a p-value $\geq$0.05 represents random variability (non-significant). If p was <0.05 (significant), concordance was evaluated. In addition, bias between low and high temperature was computed using a log-log regression fit.

Acceptance Criteria: Per the AccuTnI Design Inputs, the McNemar p-value must be non-significant ($\geq$0.05). If the p-value is significant, concordance must be $\geq$90%. Bias at the cutoffs must be $\leq$0.0084 (SD specification).

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Results: Results are provided in Table 65, Table 66, Table 67, and Table 68 below.

Analysis at 0.02 ng/mL, for all comparisons of lower temperature versus higher temperature:

Table 65: Thermal Sensitivity/Concordance Results, 0.02 ng/mL Cutoff

Analysis	McNemar p-value	% Overall Agreement	Predicted Bias (ng/mL)	Results
Low vs. High Temp.	<0.0001	93%	0.0065	Pass

Table 66: Relative Low/High Temperature Concordance, 0.02 ng/mL Cutoff

		Relative Low Temperature	
		≤0.02 ng/mL	>0.02 ng/mL
Relative High Temperature	≤0.02 ng/mL	224	7
	>0.02 ng/mL	36	337

Analysis at 0.03 ng/mL, for all comparisons of lower temperature versus higher temperature:

Table 67: Thermal Sensitivity/Concordance Results, 0.03 ng/mL Cutoff

Analysis	McNemar p-value	% Overall Agreement	Predicted Bias (ng/mL)	Results
Low vs. High Temp.	<0.0001	91%	0.0082	Pass

Table 68: Relative Low/High Temperature Concordance, 0.03 ng/mL Cutoff

		Relative Low Temperature	
		≤0.03 ng/mL	>0.03 ng/mL
Relative High Temperature	≤0.03 ng/mL	274	2
	>0.03 ng/mL	53	275

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Individual sample results are provided in Appendix 29.

Thermal Sensitivity – Low Dose Concordance Conclusion: This study demonstrated that concordance of low dose samples at the cutoffs evaluated met the acceptance criteria across multiple ambient temperature conditions.

8.14. Thermal Sensitivity – Impact on Cross-Temperature Method Comparison

Study Description: This study was designed to show that the AccuTnI assay is providing accurate results across the ambient temperature range of the assay (18°C to 28°C). This study tested 108 lithium heparin plasma patient samples. No spiked or diluted samples were used in this study. Samples were divided into three aliquots and were tested in replicates of two at each of three temperatures. The study was run on two instruments and one reagent lot at the following temperatures:

- 18 ±2°C
- 23 ±2°C
- 28 ±2°C

Data Analysis: : Individual sample results were calculated from the calibration curve established at each temperature (*i.e.,* two replicates generated at 18°C were calculated from the calibration curves at 18°C, 23°C, and 28°C for a total of six results). These six results were averaged to determine the best estimate for each sample at each temperature. Using this best estimate, between-temperature calculations using a Passing-Bablok regression were performed as follows:

- 23°C vs. 18°C
- 23°C vs. 28°C
- 28°C vs. 18°C

Acceptance Criteria: Per the AccuTnI Design Inputs, Passing-Bablok slope =1.00 ±0.10; r ≥0.95.

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Results: Results are provided in Table 69, Figure 11, Figure 12, and Figure 13. Individual sample results are provided in Appendix 30.

Table 69: Method Comparison by Temperature

Temperature Comparison	Dose Range (ng/mL)		Slope	95% CI		r-value	n
	Low	High		Lower	Upper		
18°C vs. 23°C	0.008	90.763	**1.01**	1.00	1.02	**1.00**	108
18°C vs. 28°C	0.008	90.763	**0.98**	0.98	1.00	**1.00**	108
NLC 23°C vs. 28°C	0.008	92.670	**0.97**	0.97	0.99	**1.00**	108

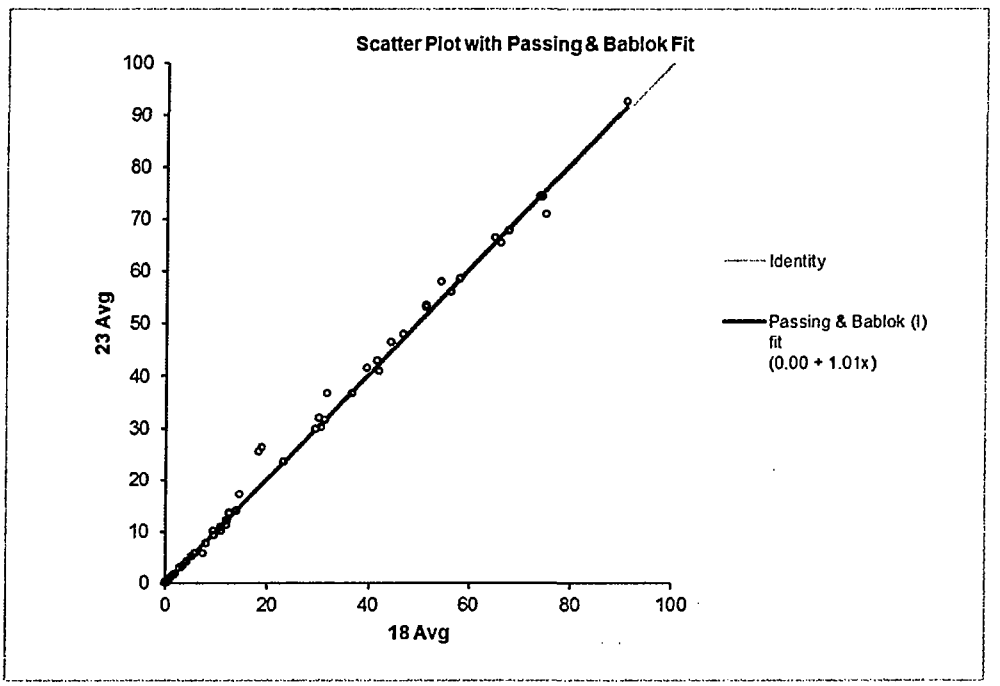

Figure 11: Passing-Bablok Plot, 18°C vs. 23°C, Concentrations in ng/mL

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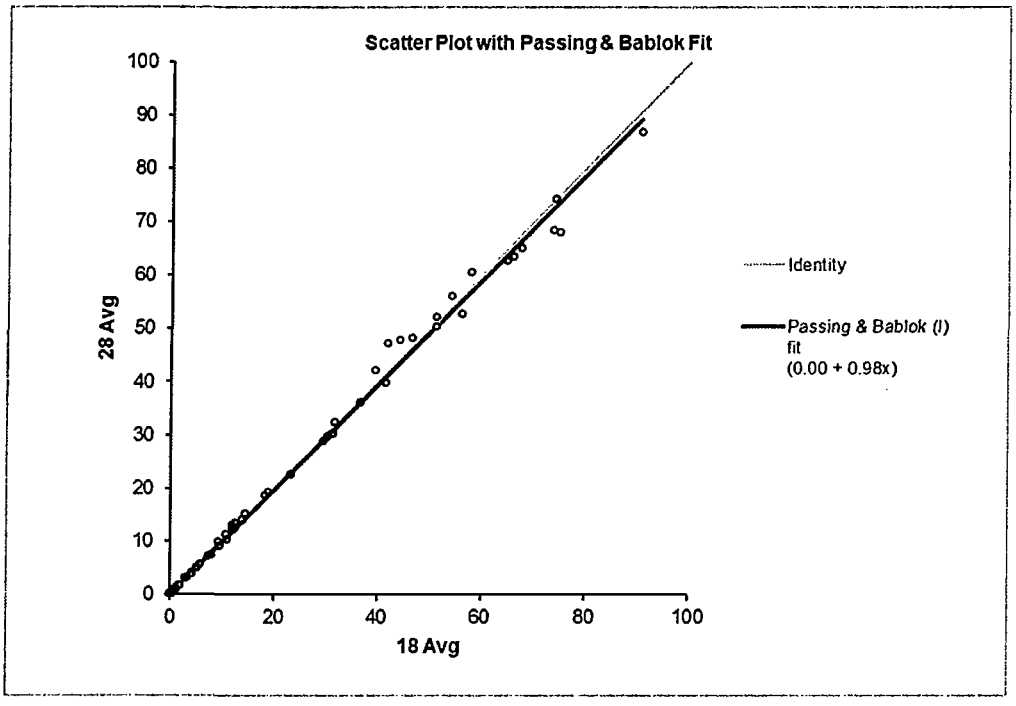

Figure 12: Passing-Bablok Plot, 18°C vs. 28°C, Concentrations in ng/mL

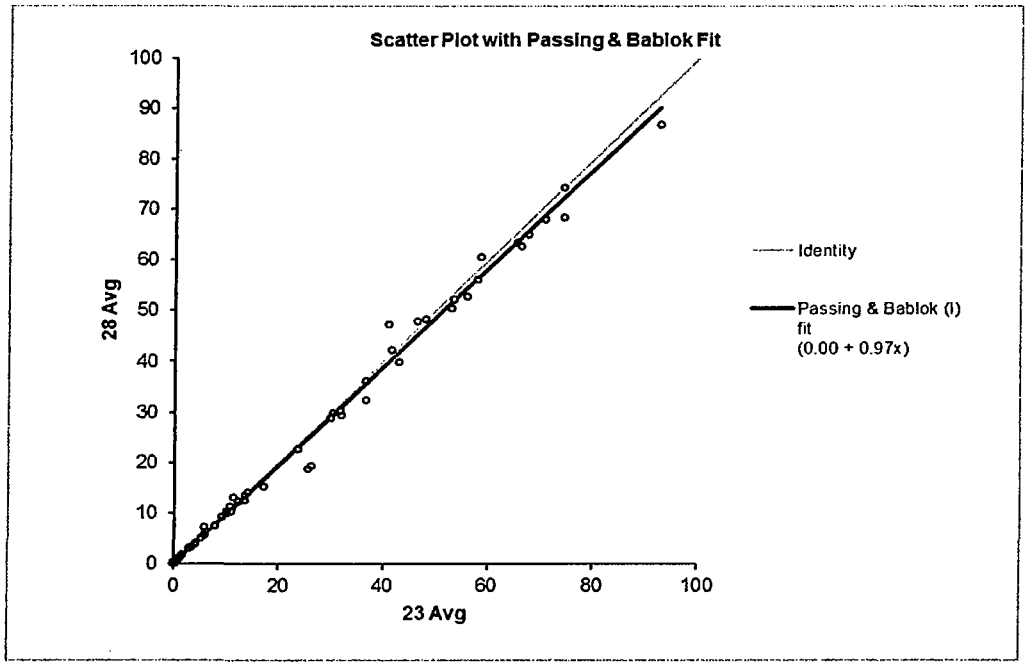

Figure 13: Passing-Bablok Plot, 23°C vs. 28°C, Concentrations in ng/mL

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Thermal Sensitivity – Cross-Temperature Method Comparison Conclusion: This study met the acceptance criteria and demonstrates that the AccuTnI assay is generating accurate results across the ambient temperature range of the assay (18°C to 28°C).

8.15. Sample Handling

Sample handling was not re-evaluated as part of this AccuTnI assay design. Appropriate sample handling is dictated by the stability of cardiac troponin I in patient samples. Different regions of the troponin I molecule demonstrate varying stability. As such, the major design feature that can impact the stability perceived by the AccuTnI assay is the specific antibody recognition sites on the native troponin I molecule.[2,3] The monoclonal antibodies and their associated epitope specificities remain unchanged for this product as compared to the previously cleared version of the assay (K010429). As such, the recognition of troponin I in patient samples and thus the stability perceived by the AccuTnI assay remain unaffected.

Appropriate sample handling guidelines were established for the cleared version of the assay.[4] Of note, the instructions in the product insert for sample handling represent conservative claims in comparison to the actual data generated in the referenced journal article. Furthermore, the claims are also conservative compared to the recommendations for refrigerated and room temperature storage cited in both the World Health Organization Use of Anticoagulants in Diagnostic Laboratory Investigations and CLSI Procedures for Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline-Fourth Edition (H18-A4). Section "Specimen Collection and Preparation" of the

[2] Katrukha AG, Bereznikova AV, Filatov VL, Esakova TV, Kolosova OV, Pettersson K, Lövgren T, Bulargina TV, Trifonov IR, Gratsiansky NA, Pulkki K, Voipio-Pulkki LM, Gusev NB. Degradation of cardiac troponin I: implication for reliable immunodetection. Clin Chem. 1998; 44(12):2433-40.

[3] Shi Q, Ling M, Zhang X, Zhang M, Kadijevic L, Liu S, Laurino JP. Degradation of cardiac troponin I in serum complicates comparisons of cardiac troponin I assays. Clin Chem 1999;45:1018–25.

[4] Venge P, Lindahl B, Wallentin L. New Generation Cardiac Troponin I Assay for the Access Immunoassay System. Clin Chem. 2001; 47(5): 959-61.

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AccuTnI assay product insert recommends handling and storage of patient samples as follows:

- ≤2 hours at room temperature (15°C - 30°C)
- ≤24 hours refrigerated
- >24 hours at -20°C or colder
- Up to 6 months at -20°C

The data provided in the original 510(k) submission for the AccuTnI assay (K010429) serves as objective evidence for the claimed, acceptable sample handling for the device addressed within this 510(k) document. No changes to the current instructions for sample handling are recommended.

8.16. Analytical Performance Conclusion

The studies presented above demonstrate the analytical performance of the AccuTnI assay met all the acceptance criteria, indicating the assay design is robust and returns results that are accurate and precise. A summary of all analytical testing is provided in Table 70 below. LoB, LoD, LoQ, and precision testing per recognized standards demonstrates analytical performance to support the current manner in which troponin testing is used clinically. Assay linearity is acceptable within the assay range. All compounds tested showed negligible interference and evidence of cross-reactivity was low.

Moreover, the extensive testing and analyses demonstrate that no clinically significant difference in results were observed due to ambient temperature fluctuations and the assay met all acceptance criteria under conditions of varying ambient temperatures, confirming the effectiveness of the thermal algorithm. These studies, in combination with the clinical trial, demonstrate the AccuTnI is substantially equivalent to the predicate device.

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Table 70: Analytical Performance Summary

Study	510(k) Section	Study Description	Acceptance Criteria	Results	Pass/Fail
Limit of Blank	8.1	18°C EP17-A	LoB ≤0.010 ng/mL	0.004 ng/mL	Pass
		NLC EP17-A		0.003 ng/mL	Pass
		28°C EP17-A		0.004 ng/mL	Pass
		Multi-Temp		0.003 ng/mL	Pass
		Cross-Temp Analysis	LoB within 0.010 ng/mL of each temp	0.001 ng/mL	Pass
Limit of Detection	8.2	18°C EP17-A	LoD ≤0.030 ng/mL	0.006 ng/mL	Pass
		NLC EP17-A		0.005 ng/mL	Pass
		28°C EP17-A		0.009 ng/mL	Pass
		Multi-Temp	SD ≤0.0084 ng/mL LoD ≤0.030 ng/mL	Max SD = 0.0038 ng/mL LoD = 0.009 ng/mL	Pass
		Cross-Temp Analysis	SD ≤0.0084 ng/mL LoD ≤0.030 ng/mL	Max SD = 0.0052 ng/mL LoD = 0.010 ng/mL	Pass
Limit of Quantitation	8.3	18°C EP17-A	10% LoQ ≤0.06 ng/mL 20% LoQ ≤0.03 ng/mL	Max 10% LoQ = 0.02 ng/mL Max 20% LoQ = 0.01 ng/mL	Pass
		NLC EP17-A		Max 10% LoQ = 0.03 ng/mL Max 20% LoQ = 0.01 ng/mL	Pass
		28°C EP17-A		Max 10% LoQ = 0.04 ng/mL Max 20% LoQ = 0.02 ng/mL	Pass
		Multi-Temp	10% LoQ ≤0.06 ng/mL 20% LoQ ≤0.03 ng/mL SD ≤0.0084 ng/mL or CV ≤8%	Max 10% LoQ = 0.03 ng/mL Max 20% LoQ = <0.01 ng/mL Max SD = 0.0047 ng/mL Max CV = 3%	Pass
		Cross-Temp Analysis	10% LoQ ≤0.06 ng/mL 20% LoQ ≤0.03 ng/mL SD ≤0.0084 ng/mL or CV ≤8%	Max 10% LoQ = 0.04 ng/mL Max 20% LoQ = 0.02 ng/mL Max SD = 0.0055 ng/mL Max CV = 4%	Pass

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Table 70: Analytical Performance Summary

Study	510(k) Section	Study Description	Acceptance Criteria	Results	Pass/Fail
Precision	**8.4**	18°C EP5-A2	SD ≤0.0084 ng/mL or CV ≤8%	Max SD = 0.0030 ng/mL Max CV = 5%	Pass
		NLC EP5-A2		Max SD = 0.0032 ng/mL Max CV = 3%	Pass
		28°C EP5-A2		Max SD = 0.0050 ng/mL Max CV = 6%	Pass
		Multi-Temp		Max SD = 0.0020 ng/mL Max CV = 6%	Pass
		Cross-Temp Analysis		Max SD = 0.0030 ng/mL Max CV = 8%	Pass
Linearity	**8.5**	18°C EP6-A	p >0.05 or bias ≤16%	Max bias = 10%	Pass
		NLC EP6-A		Max bias = 9%	Pass
		28°C EP6-A		Max bias = 8%	Pass
High Dose Hook Effect	**8.6**	NLC	No hook effect from S5 calibrator concentration up to at least 2,000 ng/mL.	No hook at 2,529 ng/mL	Pass
Reagent pack real time stability	**8.7**	NLC	Target = 12 months	Stable for 6 months; study ongoing	Pass
Reagent open pack stability			Stable for ≥35 days	Stable for 56 days	Pass
Stored calibration curve stability			Stable for ≥35 days	Stable for 56 days	Pass
Calibrator real time stability			Target = 12 months	Stable for 4 months; study ongoing	Pass
Calibrator open vial stability			Target = 60 days	Stable for 8 days; study ongoing	Pass
Interference and Analytical Specificity	**8.8**	18°C EP7-A2	Interference ≤10.0%	No interference >10.0%	Pass
		NLC EP7-A2			Pass
		28°C EP7-A2			Pass
Cross-reactivity	**8.9**	18°C EP7-A2	Cross-reactivity ≤1.00%	Max cross-reactivity = 0.11%	Pass
		NLC EP7-A2		Max cross-reactivity = 0.08%	Pass
		28°C EP7-A2		Max cross-reactivity = 0.06%	Pass
Sample Matrix Comparison	**8.10**	18°C	Slope = 1.00 ±0.10 r >0.95	Slope = 1.03, r = 0.99	Pass
		23°C		Slope = 1.02, r = 0.99	Pass
		28°C		Slope = 1.04, r = 0.99	Pass

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Table 70: Analytical Performance Summary

Study	510(k) Section	Study Description	Acceptance Criteria	Results	Pass/Fail
HAMA / Heterophile	**8.11**	NLC	Characterize blocker effectiveness	The AccuTnI reagent pack has been formulated to minimize the effects of HAMA and Heterophile interference.	Pass
Thermal Sensitivity – Robustness	**8.12**	Six Temperatures	p >0.05 or slope ≤0.010	Max slope = -0.007	Pass
Thermal Sensitivity – Impact on Low Dose Concordance / Agreement	**8.13**	Six Temperatures	p >0.05 or concordance ≥90% Bias ≤0.0084 ng/mL	0.02 ng/mL analysis: Concordance 93%, Bias = 0.0065 ng/mL 0.03 ng/mL analysis: Concordance 91%, Bias = 0.0082 ng/mL	Pass
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison	**8.14**	18°C vs 23°C	Slope = 1.00 ±0.10 r >0.95	Slope = 1.01, r = 1.00	Pass
		18°C vs 28°C		Slope = 0.98, r = 1.00	Pass
		23°C vs 28°C		Slope = 0.97, r = 1.00	Pass

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9.0 Clinical Trial

Clinical performance of the AccuTnI assay was assessed through a series of clinical studies on Access 2 instruments with Access 2 system software version 3.3 installed. The reference interval study cohort was prospectively enrolled from seven geographically diverse sites consisting of apparently healthy individuals. The feasibility efficacy study cohort of the intended use population was prospectively enrolled at the emergency department at one site. The pivotal efficacy study cohort of the intended use population was prospectively enrolled at the emergency departments of 14 geographically diverse sites. All study sites were located in the United States, and the studies were conducted according to Good Clinical Practice. The clinical performance studies are summarized in the following table.

510(k) Section	Study	Description	Result
9.8	Reference Interval Trial	Seven site prospective study of apparently healthy adults	99th percentile URL was 0.02 ng/mL
9.9	Feasibility Efficacy Trial	One site prospective study of the intended use population	ROC curve analysis estimated a cut-off of 0.03 ng/mL (0.01 -0.04 ng/mL) which yielded 95% sensitivity
9.10	Pivotal Efficacy Trial	Fourteen site prospective study of the intended use population	ROC curve analysis determined a cut-off of 0.03 ng/mL which yielded 94% (91-98%) sensitivity

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9.1. Clinical Trials Table of Contents

9.0 CLINICAL TRIAL 9-1

9.1. CLINICAL TRIALS TABLE OF CONTENTS 9-2
9.2. OBJECTIVES AND OVERVIEW OF THE CLINICAL TRIALS 9-5
9.3. INTENDED USE 9-8
9.4. INSTITUTIONAL REVIEW BOARD (IRB) AND INFORMED CONSENT 9-8
9.5. DATA QUALITY ASSURANCE 9-8
9.6. BLOOD COLLECTION, SPECIMEN TYPES, PROCESSING, STORAGE 9-9
9.7. LABORATORY TESTING 9-10
9.7.1. Precision 9-10
9.7.2. Daily Quality Control (QC) Testing Over Time 9-11
9.8. REFERENCE INTERVAL TRIAL 9-14
9.8.1. Study Objective 9-14
9.8.2. Study Sites / Investigators 9-14
9.8.3. Study Design 9-14
9.8.3.1. Study Duration 9-15
9.8.3.2. Subject Inclusion Criteria 9-15
9.8.3.3. Subject Exclusion Criteria 9-15
9.8.3.4. Statistical Analysis Methods 9-16
9.8.3.5. Specimen Testing Methods 9-16
9.8.4. Results 9-17
9.8.4.1. Number of Subjects 9-17
9.8.4.2. Demographic and Clinical Characteristics 9-18
9.8.4.3. Distribution of Troponin Values by Age and Sex 9-19
9.8.4.4. AccuTnI 99th Percentile Upper Reference Limit (URL) 9-21
9.8.5. Reference Interval Trial: Summary and Conclusions 9-21
9.9. FEASIBILITY EFFICACY TRIAL 9-22
9.9.1. Study Objectives 9-22
9.9.2. Study Site / Investigator 9-22
9.9.3. Study Design 9-22
9.9.3.1. Study Duration 9-23
9.9.3.2. Subject Inclusion Criteria 9-23
9.9.3.3. Subject Exclusion Criteria 9-23
9.9.3.4. Clinical Endpoint, Universal Definition of Myocardial Infarction (MI) 9-23
9.9.3.5. Adjudication of Clinical Endpoint 9-24
9.9.3.6. Statistical Analysis Methods 9-24
9.9.3.7. Specimen Testing Methods 9-25
9.9.4. Results 9-25
9.9.4.1. Number of Subjects by Diagnosis 9-25
9.9.4.2. Demographic and Clinical Characteristics 9-26
9.9.4.3. Distribution of Troponin Values by Diagnosis 9-27
9.9.4.4. Diagnostic Sensitivity and Specificity Results at Baseline, 1-3 Hours, 3-6 Hours, and 6-9 Hours After Admission 9-28
9.9.4.5. Diagnostic Sensitivity and Specificity by Time After Symptom Onset 9-30
9.9.4.5.1. Results < 8 Hours After Symptom Onset 9-31
9.9.4.5.2. Results ≥ 8 Hours After Symptom Onset 9-32
9.9.4.6. Determination of Cutoff Yielding 95% Diagnostic Sensitivity 9-33
9.9.5. Feasibility Efficacy Trial: Summary and Conclusions 9-35
9.10. PIVOTAL EFFICACY TRIAL 9-36
9.10.1. Study Objectives 9-36
9.10.2. Study Sites / Investigators 9-37
9.10.3. Study Design 9-39
9.10.3.1. Study Duration 9-39
9.10.3.2. Subject Inclusion Criteria 9-39

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

9.10.3.3. Subject Exclusion Criteria 9-40
9.10.3.4. Clinical Endpoint, Universal Definition of Myocardial Infarction (MI) 9-40
9.10.3.5. Adjudication of Clinical Endpoint 9-40
9.10.3.6. Statistical Sample Size Assumptions and Calculations 9-41
9.10.3.7. Statistical Analysis Methods 9-42
9.10.3.8. Pooling of Data Across Sites 9-42
9.10.3.9. Specimen Testing Methods 9-43
9.10.4. Results 9-44
9.10.4.1. Comparison of Investigational Site and Independent Central Adjudication Panel Diagnosis 9-44
9.10.4.2. Number of Subjects by Site and Diagnosis 9-45
9.10.4.3. MI Incidence by Site 9-46
9.10.4.4. Demographic and Clinical Characteristics, Overall Study Population 9-48
9.10.4.5. Demographic and Clinical Characteristics by Diagnosis 9-49
9.10.4.6. Distribution of Troponin Values By Diagnosis 9-52
9.10.4.7. Distribution of Troponin Values By Diagnosis and Sex 9-52
9.10.4.8. Distribution of Troponin Values By Diagnosis and Age 9-53
9.10.4.9. Diagnostic Sensitivity and Specificity by Time After Symptom Onset 9-54
9.10.4.9.1. Results < 8 Hours After Symptom Onset 9-56
9.10.4.9.2. Results ≥ 8 Hours After Symptom Onset 9-58
9.10.4.9.3. Results by Site / Poolability of Investigational Site Data 9-60
9.10.4.9.4. Results by Sex 9-61
9.10.4.9.5. Results by Age 9-63
9.10.4.9.6. Diagnostic Sensitivity and Specificity by Time After Symptom Onset: Summary and Conclusions 9-64
9.10.4.10. ..... Diagnostic Sensitivity and Specificity by Time After Admission 9-66
9.10.4.10.1. Results at Baseline, 1-3 Hours, 3-6 Hours, 6-9 Hours After Admission 9-68
9.10.4.10.2. Diagnostic Sensitivity and Specificity by Time After Admission: Summary and Conclusions 9-71
9.10.4.11. ..... Positive Predictive Value (PPV) and Negative Predictive Value (NPV) 9-73
9.10.4.11.1. PPV and NPV Results by Time After Symptom Onset 9-74
9.10.4.11.2. PPV and NPV Results by Time After Admission 9-75
9.10.4.11.3. PPV and NPV: Summary and Conclusions 9-76
9.10.4.12. ..... Non-MI Patients with Elevated TnI Values (Myocardial Damage) 9-78
9.10.4.12.1. Results 9-78
9.10.4.12.2. Non-MI Patients with Elevated TnI Values (Myocardial Damage): Summary and Conclusions 9-80
9.10.5. Pivotal Efficacy Trial: Summary and Conclusions 9-81
9.11. METHOD COMPARISON TO PREDICATE 9-83
9.11.1. Study Objectives 9-83
9.11.2. Study Sites / Investigators 9-83
9.11.3. Study Design 9-83
9.11.3.1. Subject Inclusion and Exclusion Criteria 9-83
9.11.3.2. Sample Size Rationale and Statistical Analysis Methods 9-83
9.11.3.3. Specimen Testing Methods 9-84
9.11.4. Results 9-85
9.11.4.1. Number of Samples 9-85
9.11.4.2. Regression Analysis and Correlation Coefficient 9-86
9.11.4.3. Concordance (% agreement) 9-87
9.11.4.4. Diagnostic Sensitivity and Specificity 9-88
9.11.4.5. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) 9-90
9.11.5. Method Comparison to Predicate: Summary and Conclusions 9-92
9.12. SAMPLE MATRIX COMPARISON (LITHIUM HEPARIN PLASMA, SERUM) 9-94
9.12.1. Study Objectives 9-94
9.12.2. Study Sites / Investigators 9-94
9.12.3. Study Design 9-94
9.12.3.1. Subject Inclusion and Exclusion Criteria 9-94
9.12.3.2. Sample Size Rationale and Statistical Analysis Methods 9-94
9.12.3.3. Specimen Testing Methods 9-95

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

9.12.4. Results *9-96*
9.12.4.1. Number of Samples 9-96
9.12.4.2. Regression Analysis and Correlation Coefficient 9-96
9.12.5. Sample Matrix Comparison: Summary and Conclusions *9-96*
9.13. ATTACHMENT I: BIBLIOGRAPHY 9-97
9.14. ATTACHMENT II: INVESTIGATIONAL SITES (SUBJECT ENROLLMENT) 9-99
9.15. ATTACHMENT III : SPECIMEN TESTING SITES (LABORATORIES) 9-103
9.16. ATTACHMENT IV: INDEPENDENT CENTRAL ADJUDICATION PANEL MEMBERS 9-104
9.17. ATTACHMENT V: FORM FDA 3454 "CERTIFICATION: FINANCIAL INTEREST AND ARRANGEMENTS OF CLINICAL INVESTIGATORS" 9-105
9.18. ATTACHMENT VI: PIVOTAL EFFICACY TRIAL PROTOCOL AND CASE REPORT FORMS 9-113
9.19. ATTACHMENT VII: CERTIFICATION OF COMPLIANCE WITH REQUIREMENTS OF CLINICALTRIALS.GOVDATA BANK 9-137

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9.2. Objectives and Overview of the Clinical Trials

- Over the past 15 years since clearance of the first troponin assay, diagnosis of myocardial infarction (MI) has evolved. The classification of MI has migrated from obsolete WHO diagnostic criteria to the current Universal Definition of MI (Thygesen K. Circulation 2007;116:2634-53). Consensus guidelines have emerged that promote the use of more sensitive troponin assays and lower cutoffs.
- In order to evaluate the clinical performance characteristics of the AccuTnI assay reflecting current clinical practice, Beckman Coulter filed a Pre-IDE with FDA in early 2010 with a proposed trial design and strategy for clearance.
- Following the guidance in "Points to Consider for Troponin pre-IDE and 510(k) submissions (April 30, 2010)" as well as written FDA feedback on our Pre-IDE submission and subsequent discussions, we now present the results of our AccuTnI clinical trials in this current submission.
- As described in the Points to Consider document, a suitable cutoff (or cutoffs) for diagnosing MI should be determined through a pilot study or other appropriate method prior to commencing the prospective pivotal trial. Suitable cutoffs were determined by conducting:
    - a prospective Reference Interval Trial (99th percentile of normal, Upper Reference Limit [URL]), and
    - a prospective Feasibility Trial of the intended use population presenting to the Emergency Department with symptoms suggestive of acute coronary syndromes (ACS)
- To evaluate the clinical performance of the AccuTnI assay in a prospective Pivotal Trial, sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were determined for serial time intervals after symptom onset and after admission to the hospital. 95% Confidence Intervals were computed. The following potential cutoffs were evaluated:
    - The 99th percentile Upper Reference Limit (URL)

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- The cutoff derived from ROC curve analysis of the Feasibility Trial results: 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) (Sensitivity 95.5% [84.5 - 99.4])
- Mild to moderate elevations of troponin: Cutoffs from 0.02 to 0.50 ng/mL

- Positive and negative predictive values are also reported.
- The table on the following page provides an overview of the AccuTnI clinical trials presented in this submission.

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Overview of Clinical Trials

Clinical Trial (Protocol #)	Subject Population	Study Objective
Reference Interval Trial (TnI-03-09)	• Healthy Donors (no cardiovascular disease) • n = 527	• To establish the 99th percentile upper reference limit (URL) in healthy adults
Feasibility Efficacy Trial (cPAPPA-1-07)	• Patients presenting to the Emergency Department (ED) with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS) (intended use population, "all-comers"). • Study endpoints are independently adjudicated. • n = 363	• To evaluate the AccuTnI assay as an aid in the diagnosis of myocardial infarction (MI). • To determine a proposed cutoff for diagnosis of MI, to be validated in the pivotal trial. • To calculate sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) over time from serial blood draws.
Pivotal Efficacy Trial (TnI-2-10)	• Patients presenting to the Emergency Department (ED) with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS) (intended use population, "all-comers") • Study endpoints are independently adjudicated. • n = 1,929	• To evaluate the AccuTnI assay as an aid in the diagnosis of myocardial infarction (MI). • To assess the 99th percentile URL. • To validate the pre-specified cutoff from the Feasibility Trial. • To calculate sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) over time from serial blood draws. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) will also be reported.
Method Comparison to Predicate Device (TnI-2-10)	• Patients/Samples from the Pivotal Efficacy Trial • (native patient samples from the intended use population with troponin values in the clinically relevant range)	• To further demonstrate substantial equivalence of the AccuTnI Assay to the predicate device, Siemens ADVIA Centaur TnI-Ultra Assay, the following analyses were performed: • Regression, correlation coefficient • Concordance (% agreement) • Sensitivity and Specificity • PPV and NPV
Matrix Comparison (TnI-2-10)	• Patients/Samples from the Pivotal Efficacy Trial	• To compare lithium heparin plasma and serum using native patient samples from the intended use population with troponin values in the clinically relevant range

Note: Lab testing of trial specimens described in Protocol TnI-03-10.

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9.3. Intended Use

- The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

9.4. Institutional Review Board (IRB) and Informed Consent

- Study protocols and informed consent forms were reviewed and approved by each site's Institutional Review Board (IRB).
- Written signed informed consent was obtained from each subject. The consent form complied with FDA regulations (Protection of Human Subjects, 21 CFR 50) and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP).

9.5. Data Quality Assurance

- A data quality assurance system was followed to ensure accurate, consistent, complete and reliable clinical trial data. Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) GCP guidelines were followed, as were Sponsor SOPs (Standard Operating Procedures) for protocols, site selection, data management, study initiation, study monitoring, close-out, and other requirements.
- Study initiation including on-site training of study staff at each site on clinical and laboratory protocols, data collection methods, sponsor monitoring plan, proposed analyses, GCPs, and other requirements.
- Sponsor monitoring staff visited sites approximately every 4 to 8 weeks throughout the study to ensure accuracy and consistency of clinical (patient medical history) and laboratory data. Study monitors regularly audited Case Report Forms (CRFs) and laboratory results against original source documentation at the study sites. Sponsor and site staff were also in regular contact via email and phone. Sponsor kept site staff aware of study progress.
- Centralized monitoring methods and data management included Electronic Data Capture (EDC) edit checks; query generation, resolution and tracking; audit

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trail; generation of listings, reports and tables; and software validation. Queries were communicated to the site and resolved frequently throughout the study.

- Original records are kept in the study files at the clinical sites (patient enrollment) and laboratory sites (specimen testing) as source documentation.

9.6. Blood Collection, Specimen Types, Processing, Storage

- Studies required collection of either a single blood sample from each subject (Reference Interval Trial) or multiple serial blood samples (Feasibility and Pivotal Efficacy Trials).
- Matched sample types, lithium heparin plasma and serum, were collected in the Pivotal Efficacy Trial for the Matrix Comparison analysis.
- Samples were collected and processed at each subject-enrollment site. Visibly hemolyzed, icteric or lipemic samples were not considered evaluable. Plasma and serum were separated from cells and dispensed into cryo tubes, stored at -20° C, then sent to Beckman Coulter for storage at -70°C. Samples were shipped to independent external laboratories for AccuTnI testing.

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9.7. Laboratory Testing

- Troponin results for the trials in this submission were determined by five external laboratory testing sites (listed in the Attachment entitled "Specimen Testing Sites").
- Laboratories were required to show proficiency in performing the AccuTnI assay (precision and daily QC testing) prior to testing the study subject specimens.
- To demonstrate proficiency, each laboratory evaluated six QC samples (3 levels of More Diagnostics Cardiac Markers controls, and 3 levels of Bio-Rad Liquichek Cardiac Markers Plus Control LT controls) in duplicate for each reagent lot twice per day for a minimum of 10 days, yielding 20 runs with 40 test results per QC per reagent lot.

9.7.1. Precision

- Precision testing in accordance with CLSI Guideline EP5-A2 (Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Addition) was performed at one external laboratory testing site. This study is also described in Section 8.4.1 (Standardized Precision study at NLC) of this submission.
- Six QC samples (3 levels of More Diagnostics Cardiac Markers controls, and 3 levels of Bio-Rad Liquichek Cardiac Markers Plus Control LT controls) were analyzed in duplicate twice per day for 20 days, yielding 40 runs (80 test results per QC sample).
- Intra-assay, inter-assay and total precision results are shown in the following table. Acceptance criteria for total precision of the AccuTnI assay were: (1) a standard deviation of less than or equal to 0.0084 for cTnI concentrations less than or equal to 0.105 ng/mL; and, (2) a CV less than or equal to 8% for cTnI concentrations greater than 0.105 ng/mL. Results showed acceptable precision at all TnI levels.

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TnI Precision SUMMARY:			Within run		Between run		Total	
Sample	n	Mean	SD	CV	SD	CV	SD	CV
BRQC1	80	0.040	0.0016	4%	0.0013	3%	0.0021	
BRQC2	80	0.626	0.0146	2%	0.0115	2%		3%
BRQC3	80	2.580	0.0551	2%	0.0279	1%		2%
MDQC1	80	0.021	0.0028	14%	0.0016	8%	0.0032	
MDQC2	80	0.963	0.0190	2%	0.0195	2%		3%
MDQC3	80	15.001	0.2686	2%	0.2015	1%		2%

9.7.2. Daily Quality Control (QC) Testing Over Time

- Results shown in the following figures reflect the mean TnI values and standard deviations obtained for a given QC sample across all reagent pilot lots and all testing sites.
- Tri-level Bio-Rad Liquichek Cardiac Markers Plus Control LT and tri-level MORE Diagnostics Cardiac Markers Control samples were analyzed in duplicate each day before specimens from study subjects were evaluated.
- The QC samples represented TnI concentrations ranging from approximately 0.02 to 15 ng/mL. Specimens from subjects enrolled in the pivotal efficacy trial and reference interval trial were analyzed over 30 days of testing.
- All results fell within the manufacturers' published QC ranges (dashed lines).
- The data demonstrate that assay performance and test results were accurate and reproducible over the course of specimen testing.

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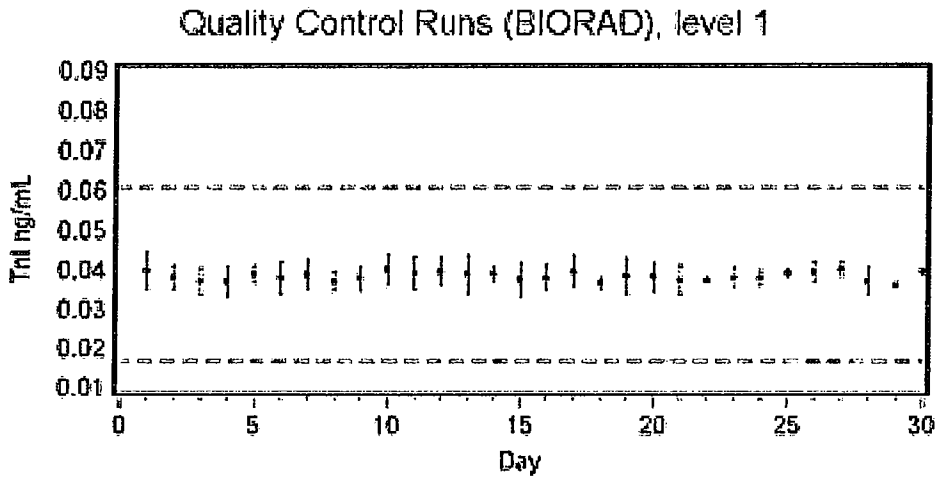
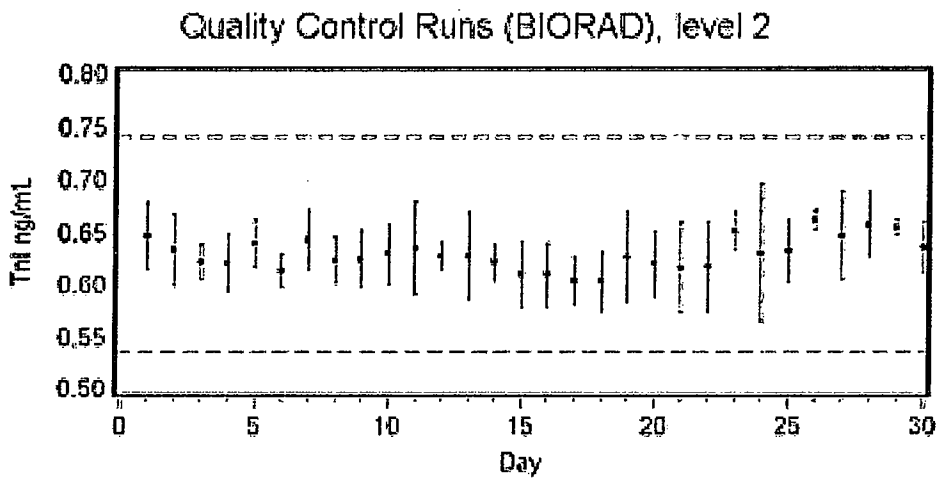
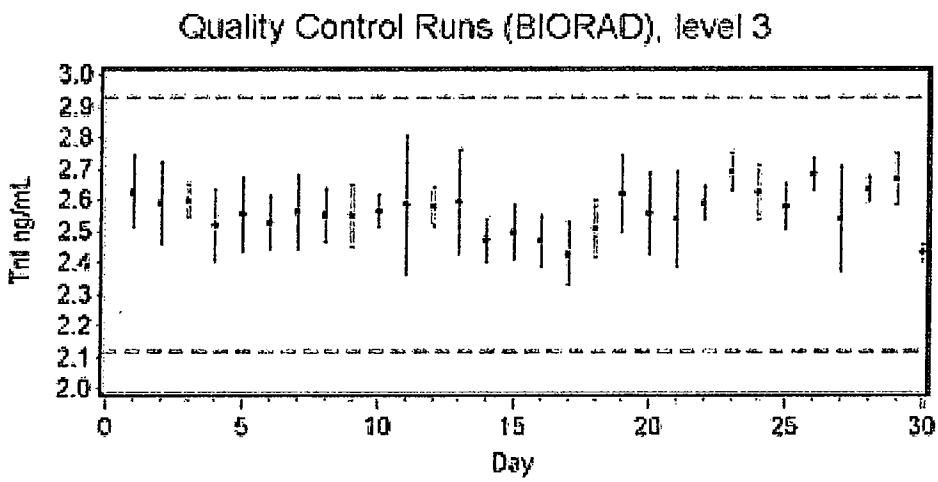
Note: Results shown reflect the mean TnI values and standard deviations obtained for a given QC sample across all reagent pilot lots and all testing sites. All results fell within the manufacturers' published QC ranges (dashed lines).







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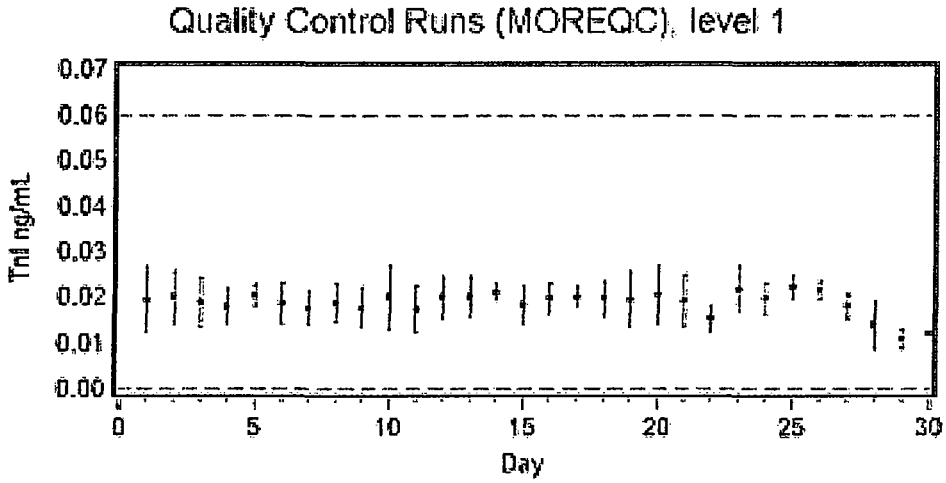
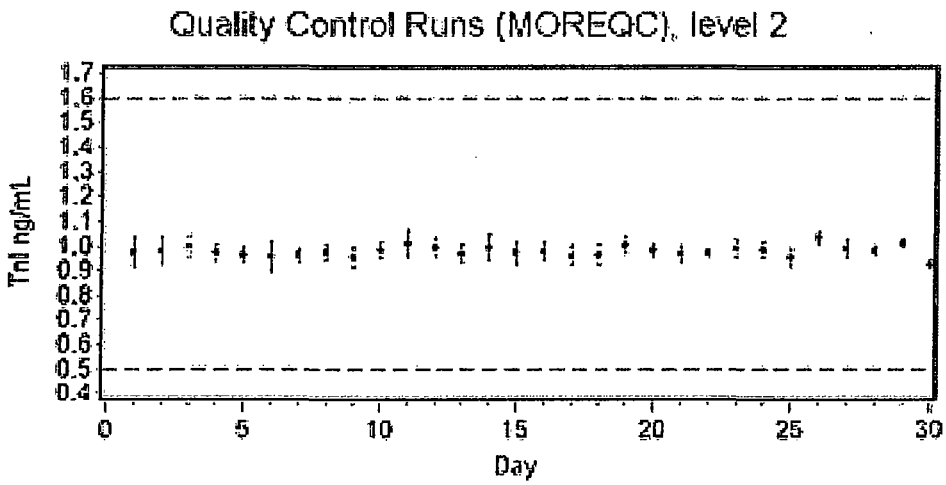
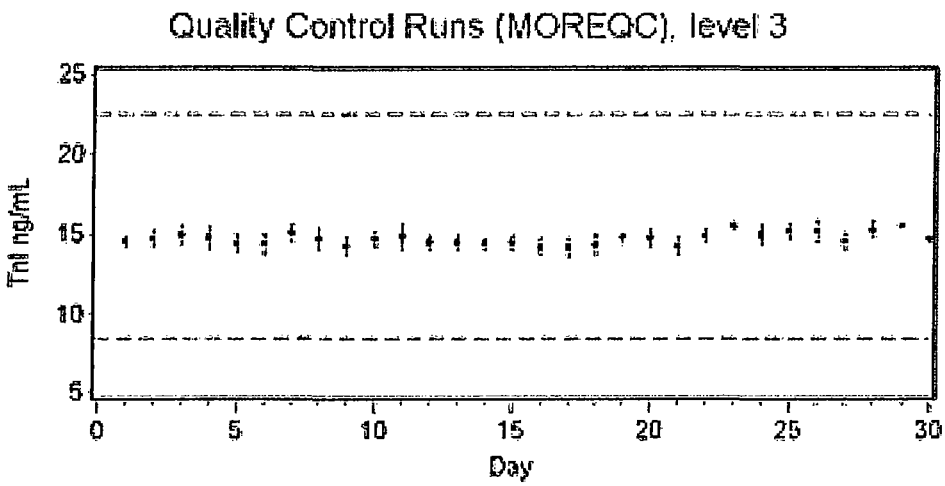
Note: Results shown reflect the mean TnI values and standard deviations obtained for a given QC sample across all reagent pilot lots and all testing sites. All results fell within the manufacturers' published QC ranges (dashed lines).







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9.8. Reference Interval Trial

9.8.1. Study Objective

- To establish the AccuTnI 99th percentile upper reference limit (URL) in healthy adults.

9.8.2. Study Sites / Investigators

- A total of 7 geographically diverse subject-enrollment-sites participated. See the Attachment entitled "Investigational Sites" for complete addresses.

Site #	Principal Investigator, Site
A	Kurtis R. Bray, PhD Clinical Research Department Beckman Coulter, San Diego, CA
B	William L. Roberts, MD, PhD Medical Director, Automated Core Laboratory ARUP Laboratories, Salt Lake City, UT
C	Mr. Sixto F. Pacheco President and CEO BioCollections Worldwide, Miami, FL
D	Denise L. Geiger, PhD, MT (ASCP), DLM (ASCP) Director of Laboratories, Clinical Chemist John T. Mather Memorial Hospital, Port Jefferson, NY
E	Alice C. Shapiro, PhD, RD, LN Clinical Principal Investigator Park Nicollet Institute, Minneapolis, MN
F	Cheryl Hodges-Savola, PhD Clinical Research Department Beckman Coulter, Chaska, MN
G	Karen E. Karn, MD, CPI Clinical Principal Investigator Ridgeview Research, Chaska, MN

9.8.3. Study Design

- This prospective multicenter trial evaluated healthy adults with no known diseases of the cardiovascular system.
- The study design meets the criteria recommended in CLSI Guideline C28-A3c: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition.

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9.8.3.1.Study Duration

- Subjects were enrolled consecutively between March 2009 and July 2010.

9.8.3.2.Subject Inclusion Criteria

- Subject is able to provide written Informed Consent
- Subject is ≥18 years of age
- Subject is apparently healthy

9.8.3.3.Subject Exclusion Criteria

- Disease(s) of/or affecting the cardiovascular system, including:
  - Hypertension
  - Angina
  - Coronary artery disease
  - History of myocardial infarction
  - History of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG)
  - Peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis
  - Hemostatic disorders (problems with platelet function and blood clotting)
  - Congestive heart failure
- Currently taking a medication for cardiovascular disease, including:
  - ACE Inhibitors (e.g. captopril [Capoten], enalapril [Vasotec], lisinopril)
  - Angiotensin II receptor blockers (e.g. Valsartan)
  - Beta-blockers (e.g. atenolol [Tenormin], metoprolol)
  - Calcium channel blockers (e.g. diltiazem, verapamil [Verelan], nifedipine [Procardia])
  - Diuretics (e.g. furosemide [Lasix], hydrochlorothiazide)
  - Blood thinners (e.g. heparin, warfarin [Coumadin])
  - Platelet inhibitors (e.g. clopidogrel [Plavix])

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- Diabetes
- Chronic kidney disease
- Other serious chronic disease(s) including:
  - Cancer or leukemia
  - Chronic Obstructive Pulmonary Disease (COPD, emphysema)
  - HIV, Hepatitis B (HBV) or Hepatitis C (HCV)
  - Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma
- Acute bacterial or viral infection, such as:
  - Bronchitis
  - Upper respiratory infection (cold, sinusitis, etc)
  - Strep throat
  - Influenza
  - Pneumonia
  - Mononucleosis
  - Oral or genital herpes outbreak
  - Urinary tract infection
- Pregnancy

9.8.3.4.Statistical Analysis Methods

- Methods followed CLSI Guideline C28-A3c: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition.
- Since TnI results do not follow a Gaussian probability distribution, a non-parametric approach (which is not distribution dependent) was used to establish the reference interval.
- The 99th percentile Upper Reference Limit (URL) of the test values obtained from a healthy population was determined using this non-parametric approach.

9.8.3.5.Specimen Testing Methods

- Samples were collected, processed, and stored at -20° C at each subject-enrollment site, then sent to Beckman Coulter for storage at

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-70°C. Samples were shipped to independent external laboratories for AccuTnI testing (Sites #1, 2, 3, listed in the Attachment entitled "Specimen Testing Sites").

- AccuTnI results were determined for lithium heparin plasma samples on the Access 2 Instrument in duplicate on 3 lots of reagent. Each subject was analyzed using the mean of duplicate results.

9.8.4. Results

9.8.4.1. Number of Subjects

- A total of 527 evaluable subjects meeting inclusion/exclusion criteria with sufficient specimen volume for testing were included in this study. Only one sample per subject was allowed.
- Enrollment by site is shown in the following table.

Site	Number of Subjects at Each Site	% of Subjects at Each Site
A	89	17%
B	99	19%
C	101	19%
D	45	9%
E	5	1%
F	94	18%
G	94	18%
Total	527	100%

Percentages may not total 100 due to rounding

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9.8.4.2. Demographic and Clinical Characteristics

- Demographic and clinical characteristics of the study population are shown in the following tables.
- The study enrolled 220 subjects <40 years of age, and 307 subjects >=40 years of age.
- The study enrolled 212 males and 315 females.

Age (years)	
N	527
Median	43
Mean ± SD	45.43 ± 16.27
Range (Minimum - Maximum)	18 - 94

Age	
< 40 years	41.7% (220/527)
>= 40 years	58.3% (307/527)

Sex	
Male	40.2% (212/527)
Female	59.8% (315/527)

Race	Percent of Subjects in Study (n/N)
White	89.9% (471/524)
Black	5.9% (31/524)
Asian	4.6% (24/524)
Other	1.5% (8/524)

Note: Race includes 9 multiracial subjects who are counted in more than one race category. Race unavailable for 3 subjects.

Ethnicity	Percent of Subjects in Study (n/N)
Hispanic or Latino	21.9% (113/515)
Not Hispanic or Latino	78.1% (402/515)

Ethnicity unavailable for 12 subjects.

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9.8.4.3. Distribution of Troponin Values by Age and Sex

- The following table shows the distribution of AccuTnI values (ng/mL) by age and sex.
- No significant differences in AccuTnI values were found between subjects <40 vs >=40 years of age (p= 0.28).
- A statistically significant difference was observed between males and females (p<0.05); however, this difference is lost in the rounding error beyond the default two significant digits reported to the customer (TnI median: males=0.001, females=0.000). Confidence intervals for the 99th percentile overlap between groups, and the statistical difference is not clinically significant as demonstrated in the "Pivotal Efficacy Trial Results" section of this submission.
- TnI results from an apparently healthy population are subject to random variation from a very small number of subjects with undetected cardiovascular disease. Note in the following graph that removal of only 3 of the 315 female subjects (those with the highest TnI values) would change the female URL from 0.02 to 0.01. Due to these random variations in enrolled study subjects, the 99th percentile URL results are not as clinically appropriate as are diagnostic cutoffs determined by ROC curve analysis of the intended use population of patients presenting to the Emergency Department (ED) with chest pain.

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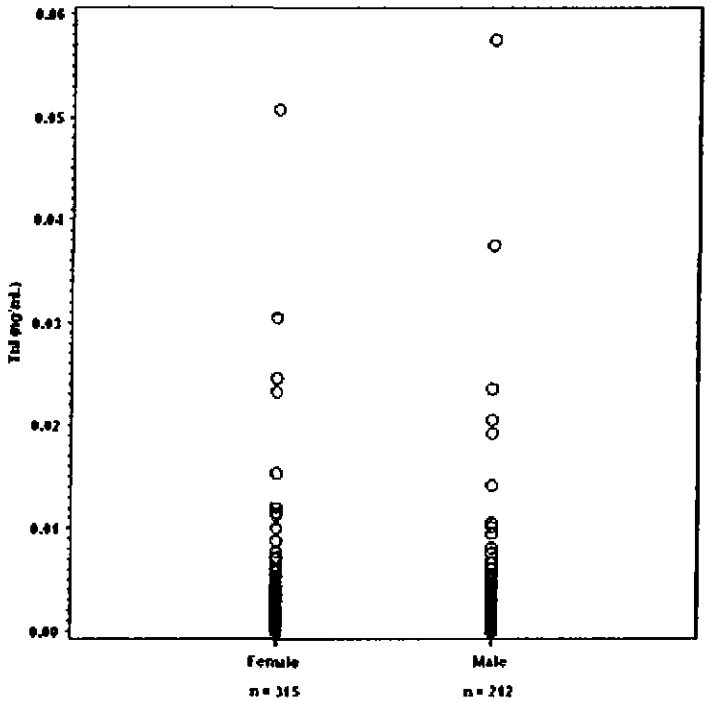
	n	Mean ± SD	Median	5th - 95th percentiles	99th percentile (95% CI)
< 40 Years	220	0.002 ± 0.005	0.000	0.000 - 0.006	0.02 (0.01 - 0.05)
>= 40 Years	307	0.002 ± 0.005	0.000	0.000 - 0.007	0.02 (0.01 - 0.06)
Males	212	0.002 ± 0.006	0.001	0.000 - 0.008	0.02 (0.01 - 0.06)
Females	315	0.002 ± 0.004	0.000	0.000 - 0.006	0.02 (0.01 - 0.05)



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9.8.4.4. AccuTnI 99th Percentile Upper Reference Limit (URL)

- The AccuTnI (ng/mL) 99th percentile Upper Reference Limit (URL) for all subjects is shown in the following table.

	n	Mean ± SD	Median	5th - 95th percentiles	99th percentile (95% CI)
All Subjects	527	0.002 ± 0.005	0.000	0.000 - 0.007	0.02 (0.01 - 0.05)

9.8.5. Reference Interval Trial: Summary and Conclusions

- The Reference Interval trial has determined the 99th percentile URL to be 0.02 ng/mL (95% CI: 0.01 - 0.05) in a population of 527 apparently healthy adults with no known diseases of the cardiovascular system.

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9.9. Feasibility Efficacy Trial

9.9.1. Study Objectives

- To evaluate the AccuTnI assay as an aid in the diagnosis of myocardial infarction (MI) in patients presenting to the Emergency Department (ED) with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS) (intended use population, "all-comers").
- To determine a proposed cutoff for diagnosis of MI, to be validated in the pivotal trial.
- To calculate diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) over time from serial blood draws.

9.9.2. Study Site / Investigator

- One clinical site participated in this prospective feasibility trial: Vanderbilt University Medical Center Emergency Department. See the Attachment entitled "Investigational Sites" for complete address.
- Vanderbilt University ED is a primary care hospital-associated facility located in a medium sized city, and sees over 50,000 patients per year with approximately 2,500 ACS evaluations. The ED is staffed by trained Emergency Medicine physicians and is a fully accredited emergency medicine facility.

Site #	Principal Investigator, Site
1	Jin Ho Han, MD, MSc Department of Emergency Medicine Vanderbilt University Medical Center Nashville, TN

9.9.3. Study Design

- This study evaluated patients presenting to the ED with chest pain or equivalent ischemic symptoms suggestive of ACS (intended use population, "all-comers").

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9.9.3.1.Study Duration

- A total of 363 ED patients with suspected ACS were enrolled consecutively in this single center prospective feasibility trial over a 12 month period.
- Serial blood samples were collected at admission (baseline) and 2 (±1) hours, and at 6 (±3) hours if standard of care patient management permitted.

9.9.3.2. Subject Inclusion Criteria

- Subject clinical history must be available for review by sponsor and FDA or other regulatory agencies
- Written Informed Consent obtained
- ≥30 years of age
- Presentation to the ED with chest discomfort or equivalent ischemic symptoms (chest pain, shortness of breath, left arm pain, lightheadedness, dizziness, weakness, and syncope) warranting an evaluation for possible ACS
- 12-lead ECG taken and cardiac biomarkers drawn at time of presentation to the ED

9.9.3.3. Subject Exclusion Criteria

- Prior participation in this study (i.e. subjects may not be enrolled more than once in this study)
- ST-segment elevation suggestive of ST-elevation myocardial infarction on initial ECG
- Recent hospitalization for an ACS within 4 weeks of enrollment
- Musculoskeletal trauma
- Secondary causes of ACS (demand ischemia)
- Known pregnancy

9.9.3.4. Clinical Endpoint, Universal Definition of Myocardial Infarction (MI)

- The clinical endpoint was diagnosis of myocardial infarction.

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- Diagnosis was based on the Universal Definition of Myocardial Infarction:
  - Detection of rise and/or fall of cardiac biomarkers (troponin)
  - With at least one value above the 99th percentile URL
  - With evidence of myocardial ischemia, with at least one of the following:
    - Symptoms of ischemia
    - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB))
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

9.9.3.5. Adjudication of Clinical Endpoint

- Diagnosis, Emergency Department: Diagnoses were determined by Emergency Medicine physicians in the Vanderbilt ED, a fully accredited emergency medicine facility with expertise in the diagnosis of MI. Clinicians were blinded to the AccuTnI assay results.
- Diagnosis, Adjudication Panel: Diagnoses were also determined by an Adjudication Panel consisting of clinicians with expertise in the diagnosis of MI. CRFs and medical records for all patients were reviewed by this panel in order to ensure standardization of diagnoses. These reviewers were blinded to the AccuTnI assay results, and were provided with the standard-of-care troponin results used at the institution for patient management. Non-agreements in diagnosis by two expert panelists were adjudicated by a third panelist.
- Statistical analyses to evaluate efficacy are based on the adjudicated diagnoses.

9.9.3.6. Statistical Analysis Methods

- To evaluate the clinical performance of the AccuTnI assay, Sensitivity (% MI correctly diagnosed) and Specificity (% Non-MI

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correctly diagnosed) were determined for serial time intervals after symptom onset and after admission to the hospital. 95% Confidence Intervals were computed. The following potential cutoffs were evaluated:

- The 99th percentile Upper Reference Limit (URL): 0.02 ng/mL
- Cutoffs from 0.02 to 0.06 ng/mL

- Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were also generated for serial time intervals. 95% Confidence Intervals were computed.
- Statistical analyses were performed using SAS System software (version 9.2), with a p value less than 0.05 indicating statistical significance. All statistical comparisons were two-tailed, and performed using Fisher's Exact test for dichotomous variables, and t-test, ANOVA, or Wilcoxon test for continuous variables depending upon data distribution and normality.

9.9.3.7. Specimen Testing Methods

- All blood samples collected were processed at the Vanderbilt core laboratory. Aliquots were stored at -70 C and batch shipped to Beckman Coulter for storage at -70°C. Samples were shipped to an independent external laboratory for AccuTnI testing (Quest Diagnostics / Specialty Laboratories, Valencia, CA, listed in the Attachment entitled "Specimen Testing Sites"). AccuTnI results were determined on the Access 2 Instrument in singlet on 1 lot of reagent.

9.9.4. Results

9.9.4.1. Number of Subjects by Diagnosis

- A total of 363 subjects were enrolled.
- Enrollment by diagnosis is shown in the following table.
- Overall MI incidence was 5.5% (20/363).

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MI	Non-MI	Total
20	343	363

9.9.4.2.Demographic and Clinical Characteristics

- Demographic and clinical characteristics are shown in the following tables for the overall population and by patient diagnosis.

Age (years)	Statistics
N	363
Median	56.00
Mean ± SD	56.84 ± 14.45
Range (Minimum - Maximum)	30.00 - 96.00

Sex	Percent of Subjects in Study (n/N)
Male	52.6% (191/363)
Female	47.4% (172/363)

Race	Percent of Subjects in Study (n/N)
White	78.9% (288/365)
Black	19.5% (71/365)
American Indian or Alaska Native	1.4% (5/365)
Other	0.3% (1/365)

Note: Race includes 2 multiracial subjects who are counted in more than one race category

Baseline Characteristics	Total (n=363)	MI (n= 20)	Non-MI (n=343)	p-value
Age, median (IQR), years	56.0 (46.0-68.0)	70.5 (59.0-77.0)	55.0 (45.0-67.0)	0.001
Sex				
Male	191/363 (52.6)	14/20 (70.0)	177/343 (51.6)	0.109
Female	172/363 (47.4)	6/20 (30.0)	166/343 (48.4)	
Race				
White	288/365 (78.9)	17/20 (85.0)	271/345 (78.6)	0.840
Black	71/365 (19.5)	3/20 (15.0)	68/345 (19.7)	
Other	6/365 (1.6)	0/20 (0.0)	6/345 (1.7)	

Note: Race includes 2 multiracial subjects who are counted in more than one race category

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9.9.4.3. Distribution of Troponin Values by Diagnosis

- The following table shows the distribution of AccuTnI values (ng/mL) by diagnosis (all subjects, all draws).
- MI subjects had significantly higher values than Non-MI subjects ($p<0.001$).

Statistic	MI	Non-MI
N	44	699
Mean ± SD	0.31 ± 0.47	0.05 ± 0.40
Median	0.12	0.03
IQR (25th - 75th percentiles)	0.08 - 0.30	0.02 - 0.04
5th - 95th percentiles	0.03 - 1.21	0.01 - 0.08

Note: N=all subjects, all draws

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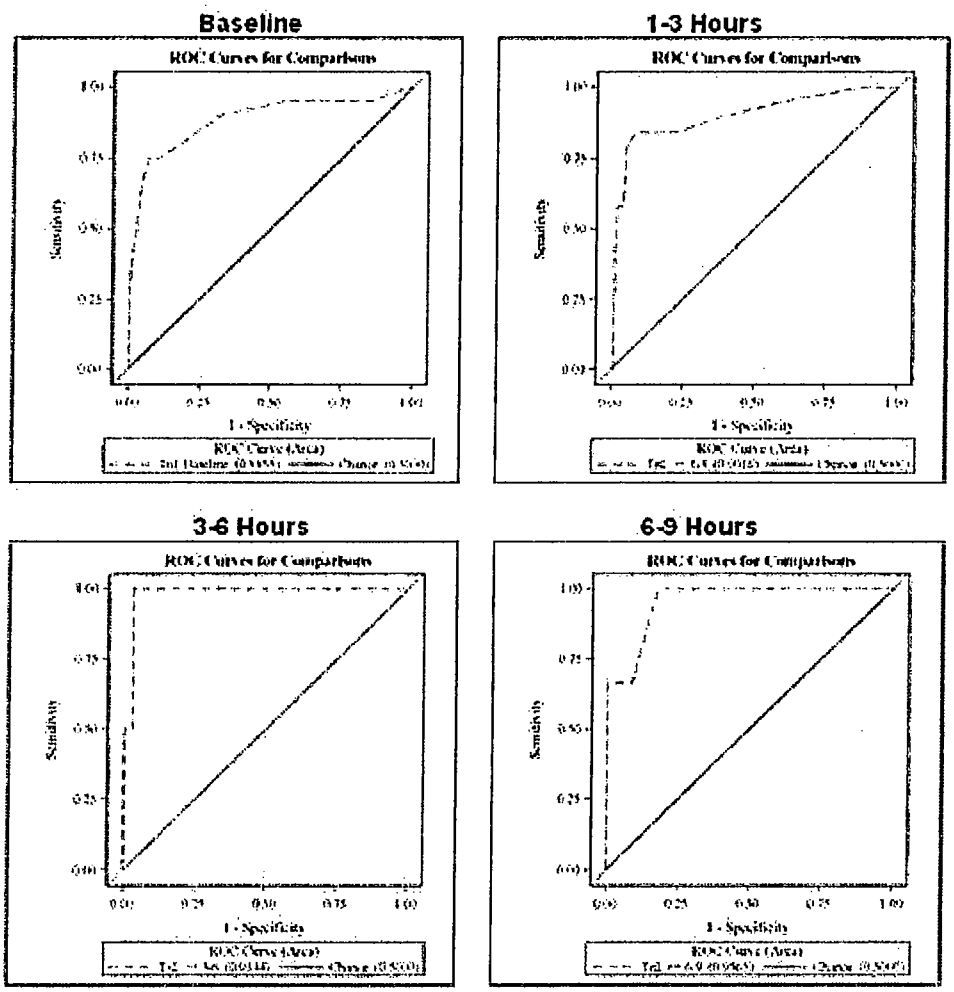
9.9.4.4. Diagnostic Sensitivity and Specificity Results at Baseline, 1-3 Hours, 3-6 Hours, and 6-9 Hours After Admission

- Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) are presented below for the Admission (Baseline) draw, and for serial time intervals after admission.
- Study results show the AccuTnI assay to have significant diagnostic efficacy at all time intervals.

Hours After Admission	AUC (95% CI)	p value
Baseline	0.89 (0.79 - 0.98)	p<0.0001
1-3 Hours	0.90 (0.81 - 0.99)	p<0.0001
3-6 Hours	0.98 (0.94 - 1.00)	p<0.0001
6-9 Hours	0.96 (0.86 - 1.00)	p<0.0001



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- Sensitivity and Specificity results are shown in the following tables for cutoffs between 0.02 and 0.06 ng/mL. (Note: Sample size decreases over time as patients are diagnosed, treated and/or discharged.)

Baseline

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	95.0	19/20	75.1 - 99.9	15.2	52/343	11.5 - 19.4
0.03	95.0	19/20	75.1 - 99.9	45.2	155/343	39.8 - 50.6
0.04	90.0	18/20	68.3 - 98.8	68.2	234/343	63.0 - 73.1
0.05	80.0	16/20	56.3 - 94.3	81.9	281/343	77.4 - 85.9
0.06	75.0	15/20	50.9 - 91.3	89.8	308/343	86.1 - 92.8

1-3 Hours

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	100	19/19	82.4 - 100.0	12.0	36/301	8.5 - 16.2
0.03	94.7	18/19	74.0 - 99.9	41.2	124/301	35.6 - 47.0
0.04	89.5	17/19	66.9 - 98.7	61.8	186/301	56.0 - 67.3
0.05	84.2	16/19	60.4 - 96.6	77.7	234/301	72.6 - 82.3
0.06	84.2	16/19	60.4 - 96.6	87.4	263/301	83.1 - 90.9

3-6 Hours

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	100	2/2	15.8 - 100.0	12.5	4/32	3.5 - 29.0
0.03	100	2/2	15.8 - 100.0	37.5	12/32	21.1 - 56.3
0.04	100	2/2	15.8 - 100.0	59.4	19/32	40.6 - 76.3
0.05	100	2/2	15.8 - 100.0	75.0	24/32	56.6 - 88.5
0.06	100	2/2	15.8 - 100.0	84.4	27/32	67.2 - 94.7

6-9 Hours

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	100	3/3	29.2 - 100.0	13.0	3/23	2.8 - 33.6
0.03	100	3/3	29.2 - 100.0	34.8	8/23	16.4 - 57.3
0.04	100	3/3	29.2 - 100.0	56.5	13/23	34.5 - 76.8
0.05	100	3/3	29.2 - 100.0	65.2	15/23	42.7 - 83.6
0.06	100	3/3	29.2 - 100.0	69.6	16/23	47.1 - 86.8

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9.9.4.5. Diagnostic Sensitivity and Specificity by Time After Symptom Onset

- Diagnostic sensitivity and specificity were also assessed by "Time After Symptom Onset" (compared to "Time After Admission" in the previous section).
- The American College of Emergency Physicians (ACEP) recommends serial troponin measurements if <8 hours after symptom onset; a single negative troponin measured ≥8 hours after symptom onset may be used to rule out MI in the ED in the context of the patient's clinical presentation and history (Fesmire FM. Ann Emerg Med. 2006;48:270-301). However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations (Thygesen K. Circulation. 2007;116:2634-53) (Thygesen K. Eur Heart J. 2010;31:2197-2204).
- Based on the ACEP symptom onset guideline recommendations, results are shown for the following time intervals:
  - <8 Hours After Symptom Onset
  - ≥8 Hours After Symptom Onset
- Note: Time from symptom onset was in some instances unavailable.

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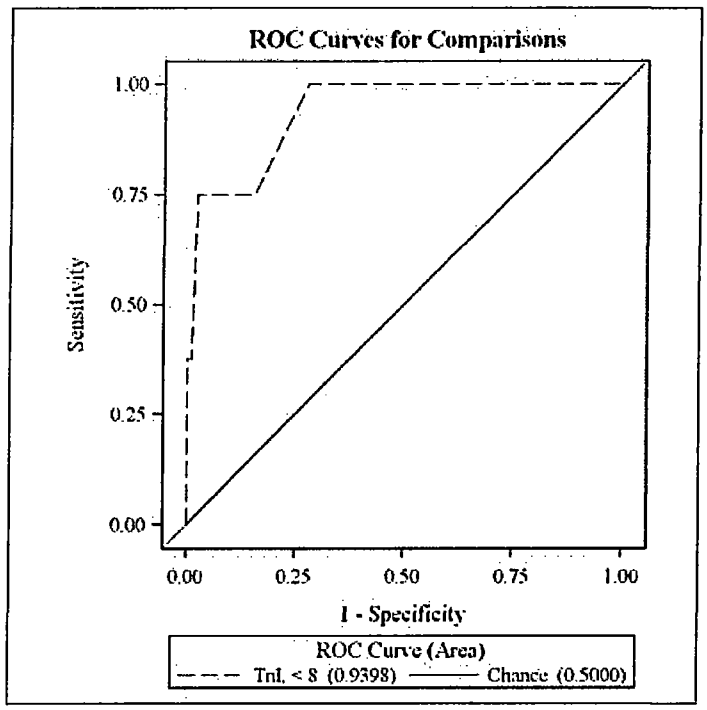
9.9.4.5.1. Results <8 Hours After Symptom Onset

- Significant diagnostic efficacy is observed for troponin measurements <8 hours after symptom onset: AUC (95% CI) = 0.94 (0.87 - 1.00), p<0.0001



	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	100	8/8	63.1 - 100.0	14.9	28/188	10.1 - 20.8
0.03	100	8/8	63.1 - 100.0	46.8	88/188	39.5 - 54.2
0.04	100	8/8	63.1 - 100.0	72.3	136/188	65.4 - 78.6
0.05	75.0	6/8	34.9 - 96.8	84.6	159/188	78.6 - 89.4
0.06	75.0	6/8	34.9 - 96.8	92.6	174/188	87.8 - 95.9

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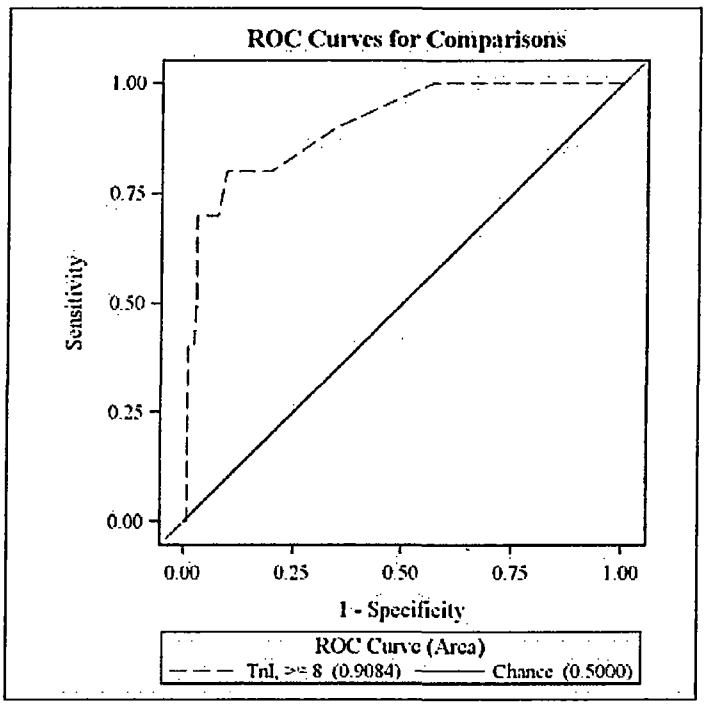
9.9.4.5.2. Results ≥8 Hours After Symptom Onset

- Significant diagnostic efficacy is observed for troponin measurements ≥8 hours after symptom onset: AUC (95% CI) = 0.91 (0.81 - 1.00), p<0.0001



	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	100	10/10	69.2 - 100.0	12.2	18/148	7.4 - 18.5
0.03	100	10/10	69.2 - 100.0	43.2	64/148	35.1 - 51.6
0.04	90.0	9/10	55.5 - 99.7	65.5	97/148	57.3 - 73.2
0.05	80.0	8/10	44.4 - 97.5	80.4	119/148	73.1 - 86.5
0.06	80.0	8/10	44.4 - 97.5	88.5	131/148	82.2 - 93.2

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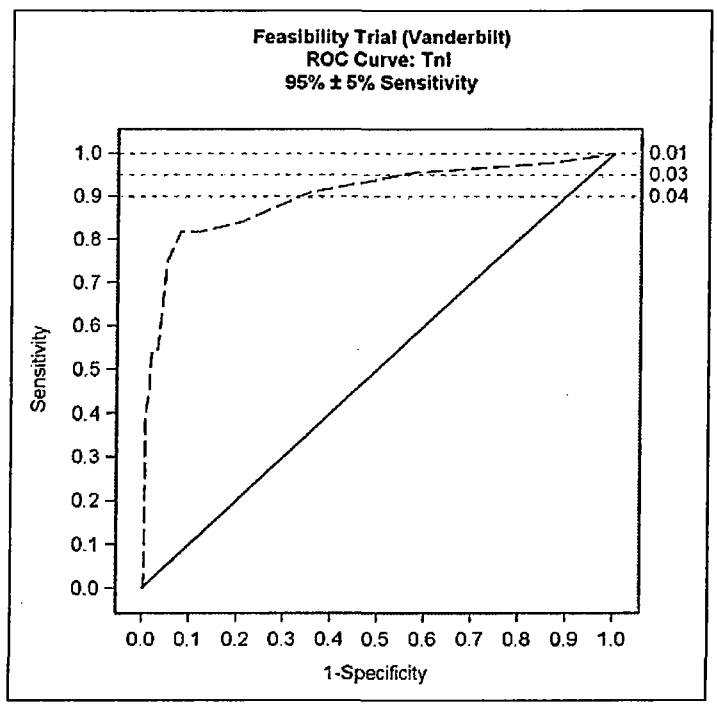
9.9.4.6. Determination of Cutoff Yielding 95% Diagnostic Sensitivity

- The prospective Feasibility Trial demonstrated significant diagnostic efficacy for the AccuTnI assay at all time intervals after admission to the ED (Baseline, 1-3 Hours, 3-6 Hours, 6-9 Hours) and after time of symptom onset (<8 Hours, ≥8 Hours).
- To determine the cutoff yielding 95% sensitivity in clinical practice where patient presentation may occur at varying times after symptom onset, and diagnosis is based on ≥2 serial draws obtained at different times after admission, an ROC curve was calculated using serial draws from all time intervals (see figure on following page).
- This analysis determined that a cutoff of 0.03 ng/mL would yield 95% sensitivity (see table on following page).
- Therefore, an estimated cutoff of 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) is proposed for validation in the Pivotal Trial, the objective of which is to determine if the cutoff that yields 95% (±5%) sensitivity is within the 95% confidence interval of results from the Feasibility Trial.



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	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	97.7	43/44	88.0 - 99.9	13.6	95/699	11.1 - 16.4
0.03	95.5	42/44	84.5 - 99.4	42.8	299/699	39.1 - 46.5
0.04	90.9	40/44	78.3 - 97.5	64.7	452/699	61.0 - 68.2
0.05	84.1	37/44	69.9 - 93.4	79.3	554/699	76.1 - 82.2
0.06	81.8	36/44	67.3 - 91.8	87.8	614/699	85.2 - 90.2

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9.9.5. Feasibility Efficacy Trial: Summary and Conclusions

- The prospective Feasibility Trial demonstrated significant diagnostic efficacy for the AccuTnI assay at all time intervals after admission to the ED (Baseline, 1-3 Hours, 3-6 Hours, 6-9 Hours) and after time of symptom onset (<8 Hours, ≥8 Hours).
- The intended use of the AccuTnI assay is to aid in the diagnosis of myocardial infarction. The clinical consequences of false negative results (irreversible myocardial damage or death) are more severe than the consequences of false positive results (unnecessary hospital admission or catheterization). Because of this, troponin assays have evolved to favor diagnostic sensitivity over specificity.
- ROC curve analysis determined that a cutoff of 0.03 ng/mL yielded 95% sensitivity. The 99th percentile URL (0.02 ng/mL) yielded 98% sensitivity.
- An estimated cutoff of 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) is proposed for validation in the Pivotal Trial, the objective of which is to determine if the cutoff that yields 95% (±5%) sensitivity is within the 95% confidence interval of results from the Feasibility Trial.
- Specificity in this feasibility trial is underestimated compared to clinical practice. The American College of Emergency Physicians (ACEP) recommends serial troponin measurements only if the patient presents soon after symptom onset; a single negative troponin measured ≥8 hours after symptom onset may be used to rule out MI in the ED (the patient is discharged). These "≥8 hours, single-sample, negative TnI" patients were not enrolled (following ACEP guidelines for rule out), decreasing the number of non-MI patients correctly diagnosed by TnI (true negatives). Therefore, specificity is underestimated in this study; true specificity would be higher in clinical practice and in studies including a greater number of these patients.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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9.10. PIVOTAL EFFICACY TRIAL

9.10.1. Study Objectives

- To evaluate the AccuTnI assay as an aid in the diagnosis of myocardial infarction (MI) in patients presenting to the Emergency Department (ED) with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS) (intended use population, "all-comers").
- To assess the 99th percentile Upper Reference Limit (URL)
- To validate the pre-specified cutoff from the Feasibility Trial
- To calculate diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) over time from serial blood draws. Positive and negative predictive values will also be reported.

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9.10.2. Study Sites / Investigators

- A total of 14 geographically diverse subject-enrollment-sites participated (listed in the following table), reflecting regional, urban, suburban and rural patient populations.
- Primary care hospital-associated emergency departments were selected. A large number of sites were recruited in order to obtain a representative intended use population overall. See the Attachment entitled "Investigational Sites" for complete addresses.

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Site #	Principal Investigator, Site
1	Jon W. Schrock, MD, FACEP, FAHA Director Clinical Decision Unit, Department of Emergency Medicine Case Western Reserve School of Medicine MetroHealth Medical Center, Cleveland, OH
2	Alan H.B. Wu, PhD, DABCC, FACB Professor, Laboratory Medicine Chief, Clinical Chemistry Laboratory, Univ of California, San Francisco San Francisco General Hospital and Trauma Center, CA
4	Deborah B. Diercks, MD, MSc Professor, Department of Emergency Medicine UC Davis Health System, Sacramento, CA
6	Alan B. Storrow, MD Associate Professor, Department of Emergency Medicine Vanderbilt University Medical Center, Nashville, TN
7	Richard M. Nowak, MD, MBA Department of Emergency Medicine Henry Ford Health System, Detroit, MI
8	Erik B. Kulstad, MD, MS Research Director, Department of Emergency Medicine Advocate Christ Medical Center, Oak Lawn, IL
9	Daniel P. Zelinski, MD, PhD Department of Emergency Medicine The Ohio State University Medical Center, Columbus, OH
10	Frank LoVecchio, DO, MPH, FACEP Research Director, Department of Emergency Medicine Maricopa Medical Center, Phoenix, AZ
11	Adam J. Singer, MD Professor and Vice-Chair for Research, Dept of Emergency Medicine State University of New York (SUNY) at Stony Brook, NY
12	Christopher J. Hogan, MD Department of Emergency Medicine Virginia Commonwealth University (VCU) Medical Center, Richmond, VA
13	Gary F. Headden, MD Medical Director, Chest Pain Center, Division of Emergency Medicine Medical University of South Carolina (MUSC), Charleston, SC
14	Christian Fromm, MD, FAAEM, FACEP Department of Emergency Medicine Maimonides Medical Center, Brooklyn, NY
15	Marna R. Greenberg, DO, MPH Department of Emergency Medicine Lehigh Valley Hospital, Allentown, PA
16	Tracie I. Shea, MD Department of Emergency Medicine Covenant Medical Center, Saginaw, MI

Note: Sites 3 and 5 were assigned site numbers but did not complete the initiation process and did not participate in the trial.

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9.10.3. Study Design

- This study evaluated patients presenting to the ED with chest pain or equivalent ischemic symptoms suggestive of ACS (intended use population, "all-comers").

9.10.3.1. Study Duration

- 1,929 consecutive subjects were enrolled prospectively by 14 Emergency Department investigational sites between September 2010 and August 2011.
- Specimen testing was performed by four external laboratory testing sites between December 2011 and February 2012.

9.10.3.2. Subject Inclusion Criteria

- Subject clinical history must be available for review by sponsor and FDA or other regulatory agencies
- Written Informed Consent obtained
- ≥21 years of age
- Presentation to the ED with chest discomfort or equivalent ischemic symptoms occurring at rest, lasting ≥5 min, and consistent with myocardial ischemia (chest pain, shortness of breath, left arm pain, lightheadedness, dizziness, weakness, and syncope)
- 12-lead ECG taken at time of presentation to the ED
- A minimum of 3 blood draws within 24 hours of presentation is desirable (collected at presentation and at every standard-of-care follow-up draw). However, 2 blood draws are acceptable when immediate intervention is required per standard-of-care, and a 3rd draw could not be obtained without delaying treatment. (Restricting the study to only those subjects with ≥3 samples would lead to selection bias by eliminating the majority of MI patients who receive timely reperfusion therapy per the American Heart Association's "Get With The Guidelines" recommendations.)

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9.10.3.3. Subject Exclusion Criteria

- Prior participation in this study (i.e. subjects may not be enrolled more than once in this study)
- Current participation in an investigational device or drug study (with the exception of other IVD blood test studies, which are acceptable)

9.10.3.4. Clinical Endpoint, Universal Definition of Myocardial Infarction (MI)

- The clinical endpoint was diagnosis of myocardial infarction.
- Diagnosis was based on the Universal Definition of Myocardial Infarction (MI) (Thygesen et al. Circulation 2007;116:2634-2653):
  - Detection of rise and/or fall of cardiac biomarkers (troponin)
  - With at least one value above the 99th percentile URL
  - With evidence of myocardial ischemia, with at least one of the following:
    - Symptoms of ischemia
    - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB))
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- The troponin assay used for diagnosis of patients at each site was an FDA-cleared TnI assay which was the standard of care at each institution.

9.10.3.5. Adjudication of Clinical Endpoint

- Diagnosis, Investigational Site: Diagnoses were determined by the site's principal investigator or clinicians with expertise in the diagnosis of MI, using all medical records for each patient. Investigators and clinicians were blinded to the AccuTnI assay results.
- Diagnosis, Independent Central Adjudication Panel: Diagnoses were also determined by an independent central Adjudication Panel consisting of clinical cardiologists with expertise in the diagnosis of MI (listed in

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the Attachment entitled "Independent Central Adjudication Panel Members"). The Panel reviewed CRFs and medical records for all patients from all sites in order to ensure standardization of diagnoses. These reviewers were blinded to the AccuTnI assay results and attending physicians' diagnosis, and were provided with the standard-of-care troponin results used at each institution for patient management. Non-agreements in diagnosis by two expert panelists were adjudicated by a third panelist.

- Statistical analyses to evaluate efficacy are based on the adjudicated diagnoses.

9.10.3.6. Statistical Sample Size Assumptions and Calculations

- The sample size required for a 95% two tailed confidence interval about a proportion is shown in the following table for possible sensitivity and specificity results.
- In the following equation, n is the sample size, z is the standard normal variate corresponding to the degree of confidence (1.96 for 95% CI), P is the estimate of sensitivity or specificity, and d is the half-width of the confidence interval (e.g. 5%):

$$n = z^2 P (1-P) / d^2$$

Sample Size (Proposed Calculation from Draft CLSI EP24)

Possible Sensitivity or Specificity Results	Minimum Sample Size Required (MI or Non-MI Patients)
95% ± 5%	**73**
90% ± 5%	**139**
85% ± 6%	136
80% ± 7%	126
70% ± 8%	126
60% ± 9%	114
50% ± 10%	96

- Assuming Diagnostic Sensitivity of **95**%, a minimum of **73 MI patients** is required.

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- Assuming Diagnostic Sensitivity of **90**%, a minimum of **139 MI patients** is required.

9.10.3.7. Statistical Analysis Methods

- To evaluate the clinical performance of the AccuTnI assay, Sensitivity (% MI correctly diagnosed) and Specificity (% Non-MI correctly diagnosed) were determined for serial time intervals after symptom onset and after admission to the hospital. 95% Confidence Intervals were computed. The following potential cutoffs were evaluated:
  - The 99th percentile Upper Reference Limit (URL): 0.02 ng/mL
  - The cutoff derived from ROC curve analysis of the Feasibility Trial results: 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) (Sensitivity 95.5% [84.5 - 99.4])
  - Mild to moderate elevations of troponin: Cutoffs from 0.02 to 0.50 ng/mL
- Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were also generated for serial time intervals. 95% Confidence Intervals were computed.
- Positive predictive value (PPV) and negative predictive value (NPV) are also reported.
- Statistical analyses were performed using SAS System software (version 9.2), with a p value less than 0.05 indicating statistical significance. All statistical comparisons were two-tailed, and performed using Fisher's Exact test for dichotomous variables, and t-test, ANOVA, or Wilcoxon test for continuous variables depending upon data distribution and normality.

9.10.3.8. Pooling of Data Across Sites

- Pooling of data across sites was determined to be justified based upon the following:

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- All sites followed a common clinical trial protocol, as outlined in the Study Design section of this submission. Subject inclusion/exclusion criteria were standardized, as were study methods.
- All specimens were tested following a standardized assay performance protocol. The laboratories demonstrated assay proficiency prior to testing patient samples, and maintained this proficiency throughout the study.
- Efficacy results were consistent across investigational sites, as shown in the Results section of this submission: "Diagnostic Sensitivity and Specificity by Time After Symptom Onset: Results by Site / Poolability of Investigational Site Data".

9.10.3.9. Specimen Testing Methods

- Samples were collected and processed at each subject-enrollment site. Visibly hemolyzed, icteric or lipemic samples were not considered evaluable. Plasma and serum were separated from cells and dispensed into cryo tubes, stored at -20° C, then sent to Beckman Coulter for storage at -70°C. Samples were shipped to independent external laboratories for AccuTnI testing.
- 1,929 consecutive subjects were enrolled prospectively by the 14 Emergency Department investigational sites between September 2010 and August 2011.
- Specimen testing was performed by four external laboratory testing sites between December 2011 and February 2012 (Sites #1, 3, 4, 5, listed in the Attachment entitled "Specimen Testing Sites").
- AccuTnI results were determined on the Access 2 Instrument in singlet, consistent with routine practice for patient specimens, using 3 lots of reagent.

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9.10.4. Results

9.10.4.1. Comparison of Investigational Site and Independent Central Adjudication Panel Diagnosis

- Diagnosis, Investigational Site: Diagnoses were determined by the site's principal investigator or clinicians with expertise in the diagnosis of MI, using all medical records for each patient. Investigators and clinicians were blinded to the AccuTnI assay results.
- Diagnosis, Independent Central Adjudication Panel: Diagnoses were also determined by an independent central Adjudication Panel consisting of clinical cardiologists with expertise in the diagnosis of MI. The Panel reviewed CRFs and medical records for all patients from all sites in order to ensure standardization of diagnoses. These reviewers were blinded to the AccuTnI assay results and attending physicians' diagnosis, and were provided with the standard-of-care troponin results used at each institution for patient management. Non-agreements in diagnosis by two expert panelists were adjudicated by a third panelist.
- Site and Panel Diagnoses, Percent Agreement
  - 1,929 consecutive subjects were prospectively enrolled. Enrollment by Site diagnosis and Adjudication Panel diagnosis is shown in the following table.
  - 94.0% (151+1656 / 1929) of Site and Panel diagnoses were in agreement.
  - Statistical analyses in this submission are based on the adjudicated diagnoses.

	Site Diagnosis		
Adjudicator Panel Diagnosis	**MI**	**Non-MI**	
MI	151 (8%)	102 (5%)	253 (13%)
Non-MI	20 (1%)	1656 (86%)	1676 (87%)
	171 (9%)	1758 (91%)	1929

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9.10.4.2. Number of Subjects by Site and Diagnosis

- In order to evaluate efficacy in a wide range of settings and patient populations, 14 geographically diverse sites were selected.
- Enrollment by site and diagnosis is shown in the following table and figure. A total of 1,929 subjects were enrolled.

Site	MI	Non-MI	Total	% of Subjects Enrolled by Each Site
01	6	53	59	3.1%
02	32	123	155	8.0%
04	35	206	241	12.5%
06	34	293	327	17.0%
07	26	243	269	13.9%
08	19	177	196	10.2%
09	1	33	34	1.8%
10	17	114	131	6.8%
11	23	135	158	8.2%
12	8	52	60	3.1%
13	20	77	97	5.0%
14	22	101	123	6.4%
15	0	4	4	0.2%
16	10	65	75	3.9%
Total	253	1676	1929	100.0%

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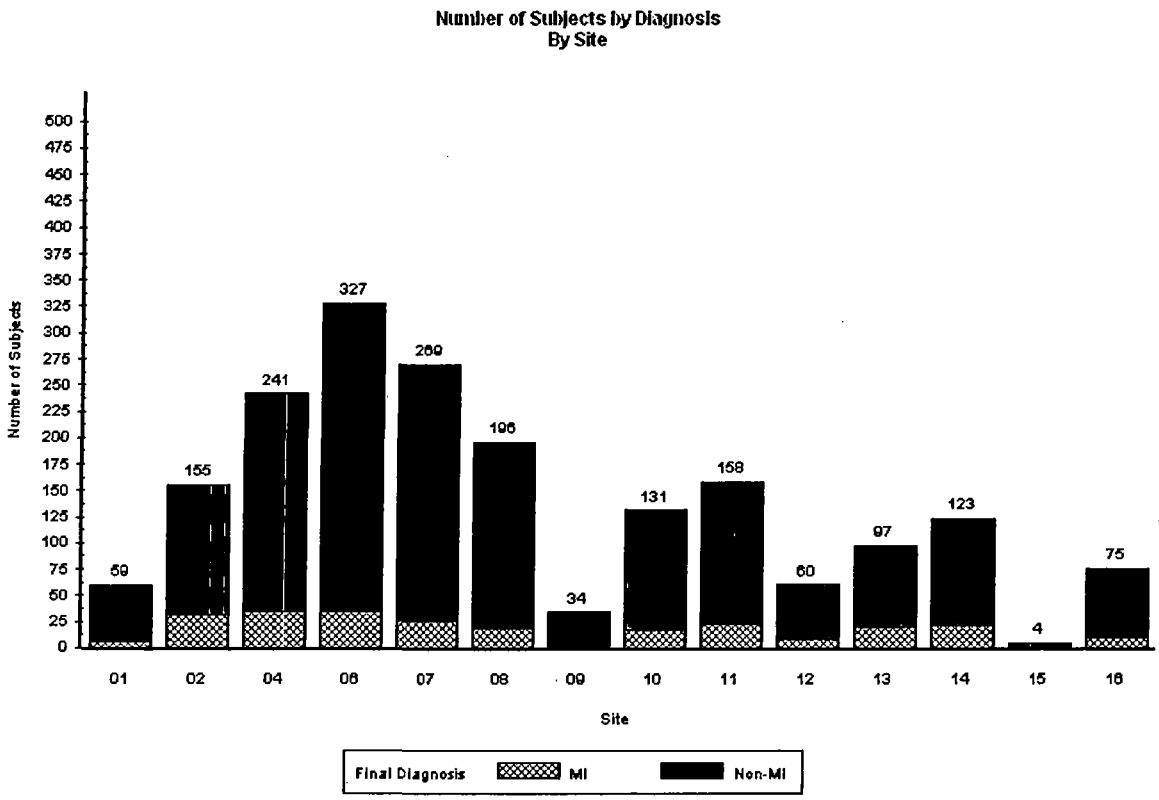

9.10.4.3. MI Incidence by Site

- The incidence of acute coronary syndromes (ACS: MI and angina) in the US in patients presenting with chest pain or equivalent ischemic symptoms in primary care hospital-associated emergency departments is approximately 20% to 25% (Jaffe AS. Clin Chem 2010;56:342-344). The incidence of MI alone is approximately 6% to 15%.
- In this current pivotal trial, overall MI incidence is 13.1%. Incidence rates varied across sites (primarily in the range of 10-15%, as shown in the following table), reflecting regional, urban, suburban and rural patient populations, which demonstrated the importance of recruiting a large number of sites in order to obtain a representative intended use population overall.
- The overall MI incidence rate in this study is consistent with literature and public health reports, and is representative of the intended use population.

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MI Incidence by Site		
Site	# of MIs/# of Subjects	MI Incidence (%)
01	6/59	10.2%
02	32/155	20.6%
04	35/241	14.5%
06	34/327	10.4%
07	26/269	9.7%
08	19/196	9.7%
09	1/34	2.9%
10	17/131	13.0%
11	23/158	14.6%
12	8/60	13.3%
13	20/97	20.6%
14	22/123	17.9%
15	0/4	0.0%
16	10/75	13.3%
Total	253/1929	13.1%

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9.10.4.4. Demographic and Clinical Characteristics, Overall Study Population

- Demographic and clinical characteristics for the overall study population are shown in the following tables.
- These data and additional cardiovascular risk factors and comorbidities are presented on the following page by diagnosis.

Age (years)	Statistics
N	1929
Median	56
Mean ± SD	57.69 ± 13.11
Range (Minimum - Maximum)	21 - 99

Sex	Percent of Subjects in Study (n/N)
Male	55.3% (1066/1929)
Female	44.7% (863/1929)

Race	Percent of Subjects in Study (n/N)
White	61.2% (1126/1839)
Black	33.8% (622/1839)
Asian	2.8% (51/1839)
American Indian or Alaska Native	0.8% (15/1839)
Native Hawaiian or Other Pacific Islander	0.4% (8/1839)
Other	1.4% (26/1839)

Race includes 9 multiracial subjects who are counted in more than one race category. Race unavailable for 90 subjects.

Ethnicity	Percent of Subjects in Study (n/N)
Hispanic or Latino	10.5% (167/1589)
Not Hispanic or Latino	89.5% (1422/1589)

Ethnicity unavailable for 340 subjects.

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9.10.4.5. Demographic and Clinical Characteristics by Diagnosis

- Complete demographic and cardiovascular risk factor data were obtained in order to fully describe and characterize the study population. These data are shown in the following tables for the overall population and by patient diagnosis.
- Patients diagnosed with MI were more likely to have known cardiovascular risk factors and comorbidities as expected, e.g. older, male, higher TIMI Risk Scores (risk factors for coronary disease), hypertension, past smoker, coronary artery disease (CAD), prior MI, heart failure, and chronic kidney disease.
- The detailed medical histories obtained in this study confirm that the subjects are representative of the intended use population presenting to the Emergency Department with ischemic symptoms suggestive of acute coronary syndromes.

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Clinical Characteristics and Cardiovascular Risk Factors, by Diagnosis Data are expressed as Median (interquartile range [IQR]), or as n/N (%)				
Baseline Characteristics and Risk Factors	***Total* (n=1929)**	***MI* (n=253)**	***Non-MI* (n=1676)**	**p-value**
Age, median (IQR), years	56.0 (49.0-66.0)	61.0 (51.0-71.0)	56.0 (49.0-65.0)	0.000
Weight, median (IQR), lbs	190.0 (160.0-222.0)	185.0 (160.0-214.0)	190.0 (160.0-224.0)	0.085
Body mass index (BMI), median (IQR)	29.3 (25.7-34.1)	28.1 (25.3-31.7)	29.6 (25.7-34.5)	0.000
Sex				
Male	1066/1929 (55.3)	180/253 (71.1)	886/1676 (52.9)	0.000
Female	863/1929 (44.7)	73/253 (28.9)	790/1676 (47.1)	
Race				
White	1126/1839 (61.2)	147/233 (63.1)	979/1606 (61.0)	0.388
Black	622/1839 (33.8)	72/233 (30.9)	550/1606 (34.2)	
Other	99/1839 (5.4)	16/233 (6.9)	83/1606 (5.2)	
Risk Factors and Comorbidities Present Prior to ED Visit				
Age >= 65 years	527/1929 (27.3)	105/253 (41.5)	422/1676 (25.2)	0.000
Family history of premature CAD (biological parents or siblings, prior to age 55)	500/1455 (34.4)	64/188 (34.0)	436/1267 (34.4)	0.921
Hypertension (HTN)	1363/1923 (70.9)	193/252 (76.6)	1170/1671 (70.0)	0.032
Dyslipidemia or Hypercholesterolemia	1023/1895 (54.0)	142/248 (57.3)	881/1647 (53.5)	0.267
Diabetes Mellitus (DM)	570/1923 (29.6)	86/253 (34.0)	484/1670 (29.0)	0.104
Current Smoker	529/1909 (27.7)	76/251 (30.3)	453/1658 (27.3)	0.329
Past Smoker	637/1863 (34.2)	99/242 (40.9)	538/1621 (33.2)	0.018
Aspirin in past 7 days	1042/1907 (54.6)	153/250 (61.2)	889/1657 (53.7)	0.025
Recent severe angina (>= 2 anginal events in last 24 hours)	742/1900 (39.1)	96/246 (39.8)	644/1654 (38.9)	0.787
ST segment deviation >= 0.5 mm on ECG at presentation	97/1921 (5.0)	40/249 (16.1)	57/1672 (3.4)	0.000
Known Coronary Artery Disease (CAD), documented stenosis > 50%	592/1863 (31.8)	112/242 (46.3)	480/1621 (29.6)	0.000
Prior Acute Myocardial Infarction (AMI)	459/1907 (24.1)	86/249 (34.5)	373/1658 (22.5)	0.000
Prior Coronary Artery Stent or Angioplasty	451/1915 (23.6)	84/250 (33.6)	367/1665 (22.0)	0.000
Prior Coronary Artery Bypass Graft (CABG)	216/1926 (11.2)	37/253 (14.6)	179/1673 (10.7)	0.065
Prior Stroke or Cerebral Vascular Accident	193/1923 (10.0)	30/253 (11.9)	163/1670 (9.8)	0.301
Heart Failure (HF)	308/1917 (16.1)	60/251 (23.9)	248/1666 (14.9)	0.000
Peripheral Vascular Disease (PVD) or Peripheral Artery Disease (PAD)	106/1904 (5.7)	25/245 (10.2)	83/1659 (5.0)	0.001
Chronic Kidney Disease or Chronic Renal Insufficiency	173/1922 (9.0)	33/253 (13.0)	140/1669 (8.4)	0.016

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Baseline Characteristics and Risk Factors	Total (n=1929)	MI (n=253)	Non-MI (n=1676)	p-value
Cardiovascular-Related Complications/Conditions During ED/Hospitalization:				
Cardiogenic shock	4/1929 (0.2)	4/253 (1.6)	0/1676 (0.0)	0.000
Atrial fibrillation/flutter (new onset)	58/1929 (3.0)	19/253 (7.5)	39/1676 (2.3)	0.000
High-degree atrioventricular block (second or third degree)	3/1929 (0.2)	0/253 (0.0)	3/1676 (0.2)	1.000
Supraventricular tachycardia (requiring treatment)	17/1929 (0.9)	8/253 (3.2)	9/1676 (0.5)	0.001
Ventricular tachycardia (requiring treatment)	4/1929 (0.2)	3/253 (1.2)	1/1676 (0.1)	0.008
Cardiotoxic drugs	38/1929 (2.0)	10/253 (4.0)	28/1676 (1.7)	0.025
Renal Failure	36/1929 (1.9)	7/253 (2.8)	29/1676 (1.7)	0.313
Heart Failure (HF)	130/1929 (6.7)	33/253 (13.0)	97/1676 (5.8)	0.000
Pulmonary Embolism	10/1929 (0.5)	0/253 (0.0)	10/1676 (0.6)	0.377
Ischemic Stroke	1/1929 (0.1)	0/253 (0.0)	1/1676 (0.1)	1.000
Transient Ischemic Attack (TIA)	4/1929 (0.2)	0/253 (0.0)	4/1676 (0.2)	1.000
Infection	25/1929 (1.3)	3/253 (1.2)	22/1676 (1.3)	1.000
TIMI risk score:				
0-2 (low risk)	1238/1929 (64.2)	122/253 (48.2)	1116/1676 (66.6)	0.000
3-4 (intermediate risk)	627/1929 (32.5)	115/253 (45.5)	512/1676 (30.5)	
5-7 (high risk)	64/1929 (3.3)	16/253 (6.3)	48/1676 (2.9)	
Cardiac-Related Medications Taken Prior to ED Visit :				
ACE Inhibitor (e.g., captopril, vasotec)	619/1898 (32.6)	88/244 (36.1)	531/1654 (32.1)	0.218
Angiotensin II receptor blocker (ARB) (e.g., valsartan)	182/1899 (9.6)	24/245 (9.8)	158/1654 (9.6)	0.904
Beta-blocker (e.g., atenolol, metoprolol)	818/1898 (43.1)	124/244 (50.8)	694/1654 (42.0)	0.009
Calcium channel blocker (e.g., diltiazem, verapamil)	390/1899 (20.5)	49/245 (20.0)	341/1654 (20.6)	0.824
Coumadin	149/1905 (7.8)	29/248 (11.7)	120/1657 (7.2)	0.015
Diuretic (e.g., furosemide, metolazone)	604/1906 (31.7)	83/248 (33.5)	521/1658 (31.4)	0.519
Low-molecular weight heparin (e.g., enoxaparin)	15/1901 (0.8)	1/247 (0.4)	14/1654 (0.8)	0.709
Nitrate (e.g., isosorbide, nitroglycerin)	399/1901 (21.0)	60/245 (24.5)	339/1656 (20.5)	0.149
Platelet inhibitor (e.g., Clopidogrel [Plavix], dipyridamole)	340/1909 (17.8)	66/248 (26.6)	274/1661 (16.5)	0.000
Statin (e.g., lovastatin, atorvastatin)	857/1907 (44.9)	131/247 (53.0)	726/1660 (43.7)	0.006
Cardiac-Related Medications During ED/Hospitalization:				
Fibrinolytic / thrombolytic (e.g. alteplase)	10/1929 (0.5)	9/253 (3.6)	1/1676 (0.1)	0.000
Unfractionated Heparin	519/1929 (26.9)	161/253 (63.6)	358/1676 (21.4)	0.000
Low-molecular weight heparin (e.g. enoxaparin)	220/1929 (11.4)	35/253 (13.8)	185/1676 (11.0)	0.192
Revascularization Procedures During Hospitalization:				
Cardiac catheterization during hospitalization	362/1929 (18.8)	140/253 (55.3)	222/1676 (13.2)	0.000
Number of Coronary Arteries or Grafts with greater than 50% occlusion	1.4±1.4	1.9±1.3	1.1±1.4	0.000
Angioplasty	87/1929 (4.5)	47/253 (18.6)	40/1676 (2.4)	0.000
Stent placement	143/1929 (7.4)	77/253 (30.4)	66/1676 (3.9)	0.000
Coronary Artery Bypass Graft (CABG)	23/1929 (1.2)	18/253 (7.1)	5/1676 (0.3)	0.000
Other percutaneous coronary intervention (PCI)	19/1929 (1.0)	14/253 (5.5)	5/1676 (0.3)	0.000
Death				
Patient death during hospitalization	9/1929 (0.5)	6/253 (2.4)	3/1676 (0.2)	0.000

Note: Race includes 9 multiracial subjects who are counted in more than one race category.
Race p-value is calculated based on counts in each race category. Race unavailable for 90 subjects.

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9.10.4.6. Distribution of Troponin Values By Diagnosis

- The following table shows the distribution of AccuTnI values (ng/mL) by diagnosis (all sites, all subjects, all draws).
- MI subjects had significantly higher values than Non-MI subjects ($p<0.0001$).

TnI Values by Diagnosis		
Statistic	MI	Non-MI
N	611	3989
Mean ± SD	1.12 ± 4.33	0.02 ± 0.40
Median	0.11	0.00
IQR (25th - 75th percentiles)	0.04 - 0.47	0.00 - 0.01
5th - 95th percentiles	0.02 - 4.99	0.00 - 0.04

Note: N=all subjects, all draws

9.10.4.7. Distribution of Troponin Values By Diagnosis and Sex

- AccuTnI showed significant diagnostic efficacy in both females and males:
- MI subjects had significantly higher values than Non-MI subjects in males ($p<0.0001$) and females ($p<0.0001$).
- Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) for males and females are presented in the "Diagnostic Sensitivity and Specificity by Time After Symptom Onset" efficacy results section of this submission.

TnI Median (Interquartile Range IQR) by Diagnosis and Sex		
Sex	MI	Non-MI
Male	0.12 (0.05-0.51)	0.00 (0.00-0.01)
Female	0.08 (0.04-0.35)	0.00 (0.00-0.01)

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9.10.4.8. Distribution of Troponin Values By Diagnosis and Age

- AccuTnI showed significant diagnostic efficacy in both younger and older patients:
- MI subjects had significantly higher values than Non-MI subjects for ages <65 years ($p<0.0001$) and ≥65 years ($p<0.0001$).
- ROC curves and AUCs for younger and older patients are presented in the "Diagnostic Sensitivity and Specificity by Time After Symptom Onset" efficacy results section of this submission.

TnI Median (Interquartile Range IQR) by Diagnosis and Age		
Age	MI	Non-MI
<65	0.10 (0.04-0.35)	0.00 (0.00-0.01)
>=65	0.13 (0.05-0.60)	0.01 (0.00-0.02)

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9.10.4.9. Diagnostic Sensitivity and Specificity by Time After Symptom Onset

- To evaluate the clinical performance of the AccuTnI assay, Sensitivity (% MI correctly diagnosed) and Specificity (% Non-MI correctly diagnosed) were determined for:
  - The 99th percentile Upper Reference Limit (URL)
  - The cutoff derived from ROC curve analysis of the Feasibility Trial results: 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) (Sensitivity 95.5% [84.5 - 99.4])
  - Mild to moderate elevations of troponin: Cutoffs from 0.02 to 0.50 ng/mL
- Sensitivity and specificity results for these cutoffs are shown in the tables on the following pages. Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) are also presented.
- The American College of Emergency Physicians (ACEP) recommends serial troponin measurements if <8 hours after symptom onset, and suggests that a single negative troponin measured ≥8 hours after symptom onset may be used to rule out MI in the ED in the context of the patient's clinical presentation and history (Fesmire FM. Ann Emerg Med. 2006;48:270-301). However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations (Thygesen K. Circulation. 2007;116:2634-53) (Thygesen K. Eur Heart J. 2010;31:2197-2204).
- Based on the ACEP symptom onset guideline recommendations, results are shown for the following time intervals:
  - <8 Hours After Symptom Onset
  - ≥8 Hours After Symptom Onset
- Note: N's do not add to the total number of subjects due to serial draws - with samples from a single subject in multiple time intervals. If more than one draw was obtained for a particular subject within any

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specific time interval, the analysis included only one sample per subject per time interval. Thus, a single subject can appear in multiple time intervals but no more than once in each time interval. In addition, time from symptom onset was in some instances unavailable.

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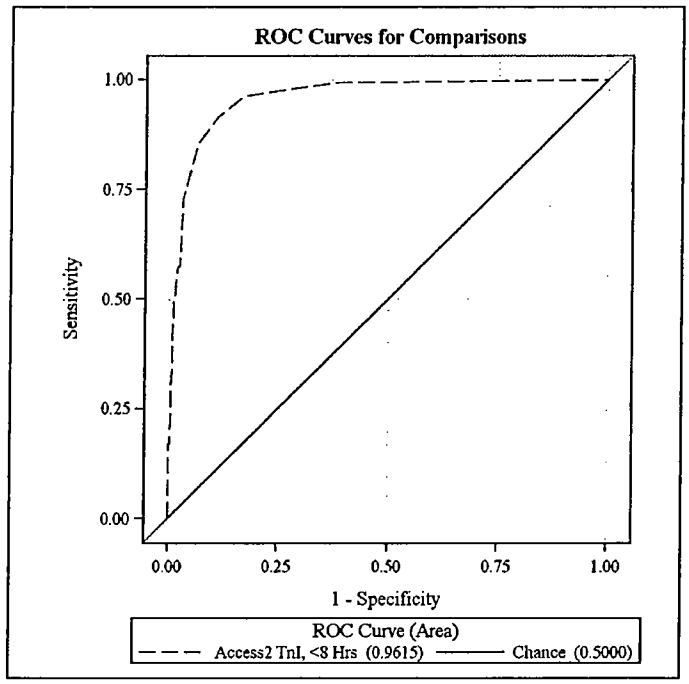
9.10.4.9.1. Results <8 Hours After Symptom Onset

- Significant diagnostic efficacy is observed for troponin measurements <8 hours after symptom onset: AUC 0.96 (95% CI: 0.95 - 0.97), p<0.0001



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- The cutoff determined in the Feasibility Trial (0.03 ng/mL) yielded 91.5% sensitivity and 89.1% specificity for troponin measurements <8 hours after symptom onset.
- The URL (0.02 ng/mL) yielded 96.4% sensitivity and 83.2% specificity.

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	96.4	159/165	93.5 - 99.2	83.2	826/993	80.9 - 85.5
0.03	91.5	151/165	87.3 - 95.8	89.1	885/993	87.2 - 91.1
0.04	85.5	141/165	80.1 - 90.8	93.6	929/993	92.0 - 95.1
0.05	78.2	129/165	71.9 - 84.5	95.5	948/993	94.2 - 96.8
0.06	72.7	120/165	65.9 - 79.5	96.9	962/993	95.8 - 98.0
0.10	53.9	89/165	46.3 - 61.5	98.3	976/993	97.5 - 99.1
0.20	40.6	67/165	33.1 - 48.1	99.2	985/993	98.6 - 99.8
0.30	28.5	47/165	21.6 - 35.4	99.5	988/993	99.1 - 99.9
0.40	24.8	41/165	18.3 - 31.4	99.5	988/993	99.1 - 99.9
0.50	20.6	34/165	14.4 - 26.8	99.6	989/993	99.2 - 100.0

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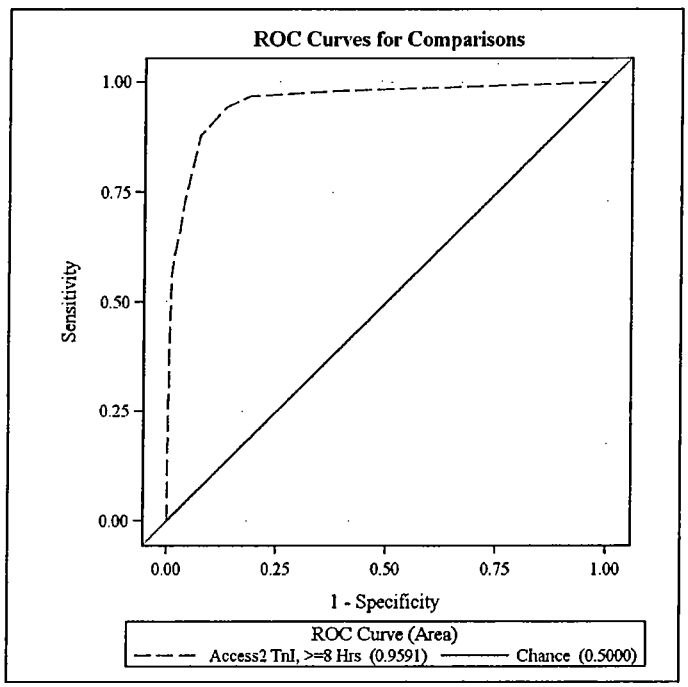
9.10.4.9.2. Results ≥8 Hours After Symptom Onset

- Significant diagnostic efficacy is observed for troponin measurements ≥8 hours after symptom onset: AUC 0.96 (95% CI: 0.94 - 0.98), p<0.0001



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- The cutoff determined in the Feasibility Trial (0.03 ng/mL) yielded 94.3% sensitivity and 86.8% specificity for troponin measurements ≥8 hours after symptom onset.
- The URL (0.02 ng/mL) yielded 96.9% sensitivity and 81.7% specificity.

	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	96.9	154/159	94.1 - 99.6	81.7	909/1113	79.4 - 83.9
0.03	94.3	150/159	90.7 - 97.9	86.8	966/1113	84.8 - 88.8
0.04	88.1	140/159	83.0 - 93.1	92.7	1032/1113	91.2 - 94.2
0.05	79.2	126/159	72.9 - 85.5	94.9	1056/1113	93.6 - 96.2
0.06	73.0	116/159	66.1 - 79.9	96.3	1072/1113	95.2 - 97.4
0.10	60.4	96/159	52.8 - 68.0	98.7	1099/1113	98.1 - 99.4
0.20	47.8	76/159	40.0 - 55.6	99.4	1106/1113	98.9 - 99.8
0.30	39.0	62/159	31.4 - 46.6	99.6	1109/1113	99.3 - 100.0
0.40	36.5	58/159	29.0 - 44.0	99.6	1109/1113	99.3 - 100.0
0.50	31.4	50/159	24.2 - 38.7	99.6	1109/1113	99.3 - 100.0

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9.10.4.9.3. Results by Site / Poolability of Investigational Site Data

- Pooling of data across sites was determined to be justified based upon the following:
  - All sites followed a common clinical trial protocol, as outlined in the Study Design section of this submission. Subject inclusion/exclusion criteria (intended use population) were standardized, as were study methods.
  - All specimens were tested following a standardized assay performance protocol. The laboratories demonstrated assay proficiency prior to testing patient samples, and maintained this proficiency throughout the study.
  - Significant diagnostic efficacy is observed at all clinical trial sites, as shown in the following table and figure for troponin measurements ≥8 hours after symptom onset.
  - No significant differences in efficacy AUCs were seen between sites (p ≥0.19).

Site	AUC (95% CI)	p value
2	0.95 (0.88 - 1.00)	p<0.0001
4	0.95 (0.92 - 0.99)	p<0.0001
6	0.96 (0.90 - 1.00)	p<0.0001
7	0.97 (0.95 - 0.99)	p<0.0001
8	0.96 (0.92 - 1.00)	p<0.0001
10	0.99 (0.98 - 1.00)	p<0.0001
11	0.96 (0.92 - 1.00)	p<0.0001
13	0.94 (0.85 - 1.00)	p<0.0001
14	0.97 (0.92 - 1.00)	p<0.0001
1,9,12,15,16	0.94 (0.86 - 1.00)	p<0.0001
All Sites	0.96 (0.94 - 0.98)	p<0.0001

Note: Sites 3 and 5 were assigned site numbers but did not participate in the trial.
The lowest enrolling sites (1,9,12,15,16) were combined into one category; the number of MI's at each site (≤10) was not sufficient to support the validity of the model fit when included separately.

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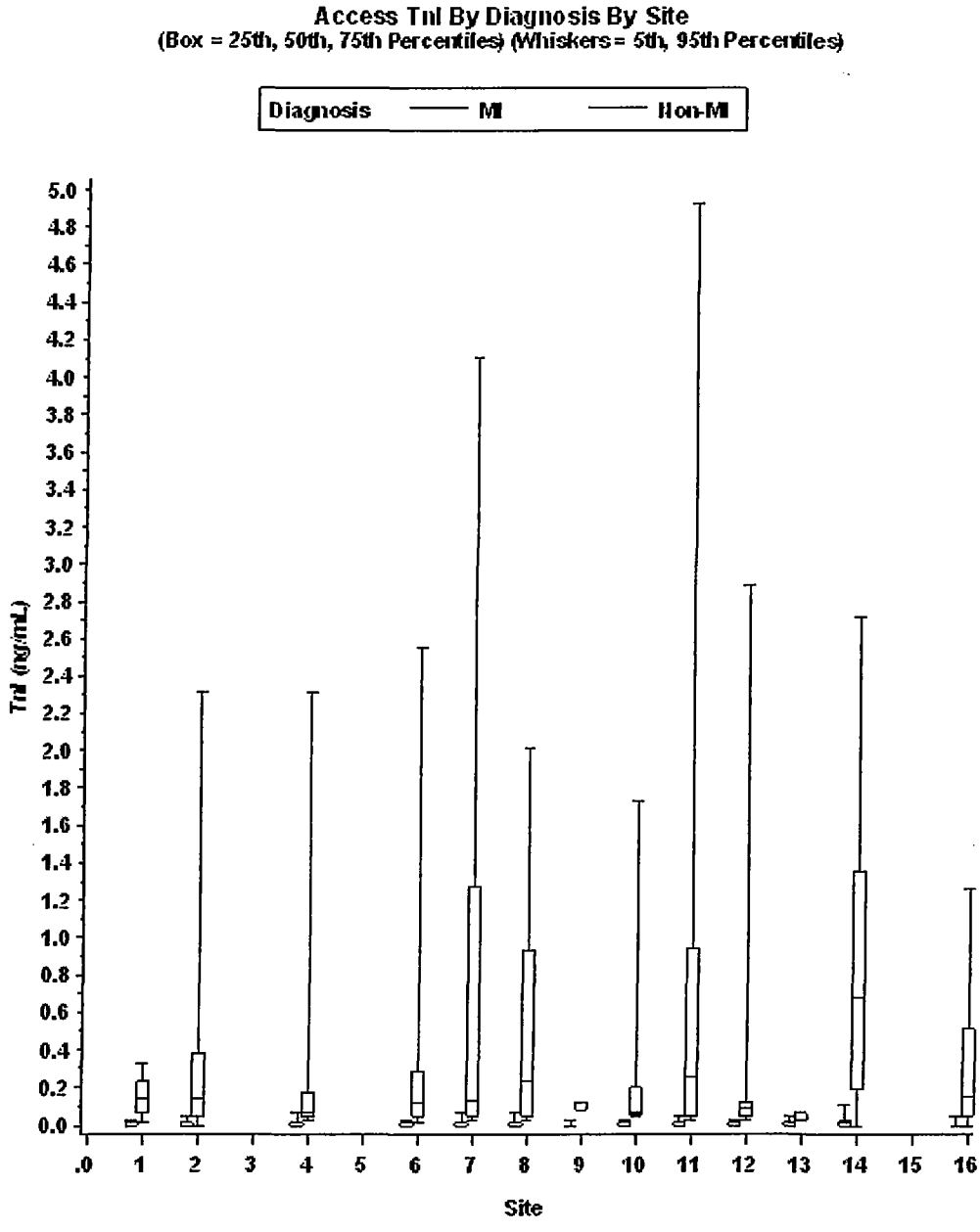
- Troponin values were significantly higher for MI than Non-MI patients at each clinical trial site (p<0.0001), as shown in the following figure. (Note: Sites 3 and 5 were assigned site numbers but did not participate in the trial. Site 15 not included [total n=4, zero MI's]).



9.10.4.9.4. Results by Sex

- Significant diagnostic efficacy was observed for both males (p<0.0001) and females (p<0.0001), as shown in the following

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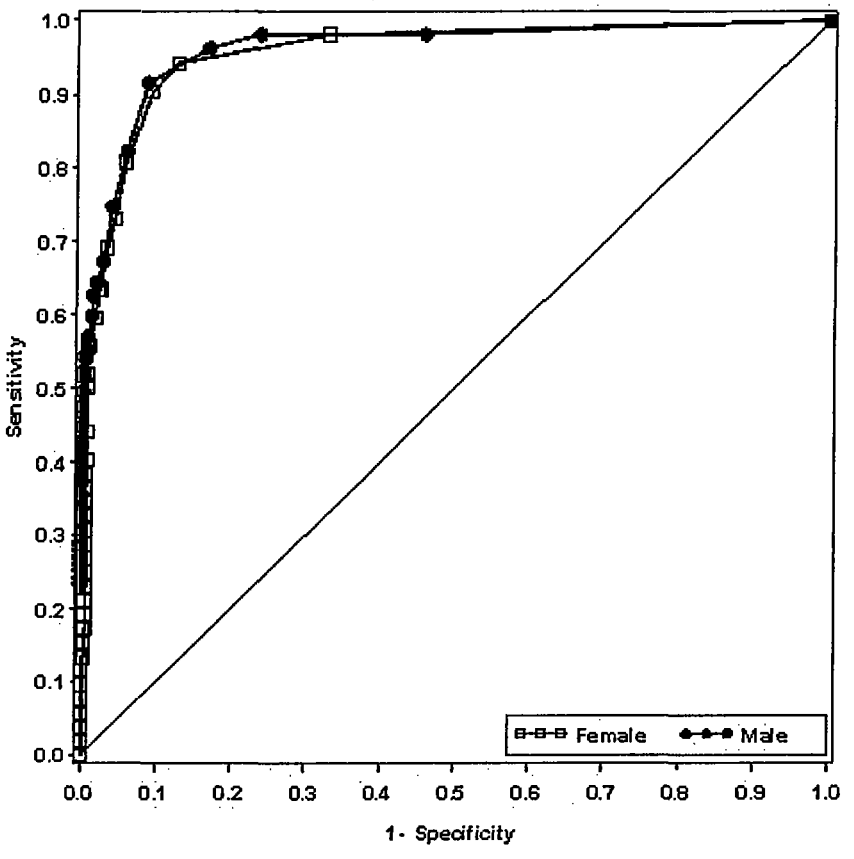
table and figure for troponin measurements ≥8 hours after symptom onset.

- Males and females were not significantly different (p = 0.76).

Sex	N_{Total}	N_{MI}	$N_{Non\text{-}MI}$	AUC (95% CI)	p-value
Female	589	52	537	0.96 (0.93 - 0.98)	p<0.0001
Male	683	107	576	0.96 (0.94 - 0.98)	p<0.0001
Total	1272	159	1113	0.96 (0.94 - 0.98)	Females vs Males p=0.76



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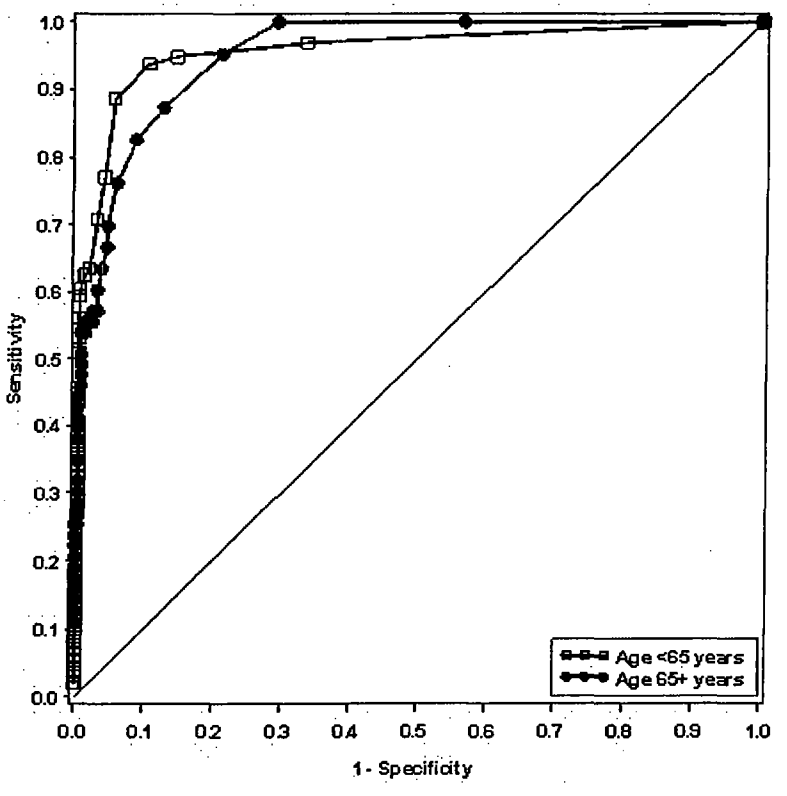
9.10.4.9.5. Results by Age

- Significant diagnostic efficacy was observed for both younger ($p<0.0001$) and older ($p<0.0001$) patients, as shown in the following table and figure for troponin measurements ≥8 hours after symptom onset.
- Younger and older patients were not significantly different ($p = 0.90$).

Age	N_{Total}	N_{AMI}	$N_{Non\text{-}AMI}$	AUC (95% CI)	p-value
Age <65 years	914	96	818	0.96 (0.93 - 0.98)	p<0.0001
Age ≥65 years	358	63	295	0.96 (0.94 - 0.98)	p<0.0001
Total	1272	159	1113	0.96 (0.94 - 0.98)	Younger vs Older p=0.90



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9.10.4.9.6. Diagnostic Sensitivity and Specificity by Time After Symptom Onset: Summary and Conclusions

- The following table summarizes the ROC AUCs for time after symptom onset.

Hours After Symptom Onset	AUC (95% CI)
< 8 Hours	0.96 (0.95 - 0.97)
≥ 8 Hours	0.96 (0.94 - 0.98)

- Significant diagnostic efficacy was observed at all clinical trial sites, for males and females, and for younger (<65 years) and older (≥65 years) patients. No significant differences were seen between sites, sexes, or age groups.
- Diagnostic sensitivity and specificity of the AccuTnI assay are summarized in the following table. Results show improved sensitivity over time as expected based upon troponin kinetics: literature reports have shown that cardiac troponin begins to rise 3-4 hours after the onset of myocardial injury, peaks at 10-24 hours, and remains increased for up to 4-7 days. The American College of Emergency Physicians (ACEP) recommends serial troponin measurements and suggests that a single negative troponin measured ≥8 hours after symptom onset may be used to rule out MI in the ED. However, patient estimates of symptom timing may not be reliable, prompting serial sampling recommendations at admission and 6-9 hours later.
- 0.02 ng/mL (URL): Sensitivity was high but specificity was near 80%.
- 0.03 ng/mL (cutoff derived in the Feasibility Trial): Sensitivity was 94% ≥8 hours after symptom onset, and specificity approached 90%.

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Cutoff	Hours After Symptom Onset	Sensitivity (95% CI)	Specificity (95% CI)
0.02 ng/mL	< 8 Hours	96% (94-99)	83% (81-86)
	≥ 8 Hours	97% (94-99)	82% (79-84)
0.03 ng/mL	< 8 Hours	92% (87-96)	89% (87-91)
	≥ 8 Hours	94% (91-98)	87% (85-89)

- The Feasibility Trial ROC curve analysis determined that a cutoff of 0.03 ng/mL (95% CI 0.01 - 0.04) yielded 95% sensitivity. This cutoff was validated by this larger multicenter Pivotal Trial: A cutoff of 0.03 ng/mL yielded 94% (91-98%) sensitivity. This 0.03 ng/mL cutoff is within the 95% Confidence Interval of results from the Feasibility Trial.

AccuTnI Cutoffs Yielding 95% Sensitivity

Feasibility Trial (Proposed 95% CI range to be validated in Pivotal Trial)	Pivotal Trial
0.03 (0.01 - 0.04) ng/mL	0.03 ng/mL

- Therefore, the Pivotal Trial results are in agreement with the Feasibility Trial results, and both trials have demonstrated significant diagnostic efficacy for the AccuTnI assay.
- The AccuTnI assay is intended for use as an aid in the diagnosis of myocardial infarction. A cutoff of 0.03 ng/mL is recommended.
- The AccuTnI assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury (Universal Definition of MI: Thygesen K. Circulation 2007;116:2634-53).

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9.10.4.10. Diagnostic Sensitivity and Specificity by Time After Admission

- Diagnostic sensitivity and specificity were also assessed by "Time After Admission" (compared to "Time After Symptom Onset" in the previous sections).
- The following cutoffs were evaluated:
  - The 99th percentile Upper Reference Limit (URL): 0.02 ng/mL
  - The cutoff derived from ROC curve analysis of the Feasibility Trial results: 0.03 ng/mL (95% CI range 0.01 to 0.04 ng/mL) (Sensitivity 95.5% [84.5 - 99.4])
  - Mild to moderate elevations of troponin: Cutoffs from 0.02 to 0.50 ng/mL
- Sensitivity and specificity results for these cutoffs are shown in the tables on the following pages. Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) are also presented.
- The recent ESC/ACC/AHA/WHF guidelines for the diagnosis of patients with myocardial infarction recommend a baseline sample upon ED arrival and a second sample 6-9 hours after presentation. MI may be ruled out in patients with negative serial marker results through the 6-9-hour period after presentation (Thygesen K. Circulation 2007;116:2634-53), (Thygesen K. Eur Heart J 2010;31:2197-2204).
- Literature reports have questioned the requirement for a 6-hour interval between first and second draws, and some have recommended troponin measurements at 3 hours after admission in order to allow for an earlier diagnosis of MI (MacRae AR. Clin Chem 2006;52:812-818).

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- Based on these guideline and literature recommendations, results are shown for the following time intervals:
  - Admission (Baseline, Time 0)
  - 1 to 3 Hours
  - 3 to 6 Hours
  - 6 to 9 Hours

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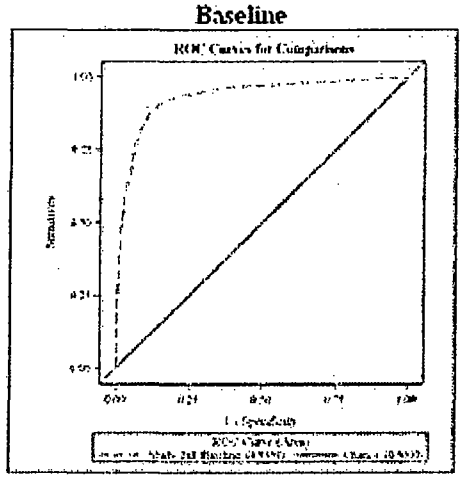
9.10.4.10.1. Results at Baseline, 1-3 Hours, 3-6 Hours, 6-9 Hours After Admission

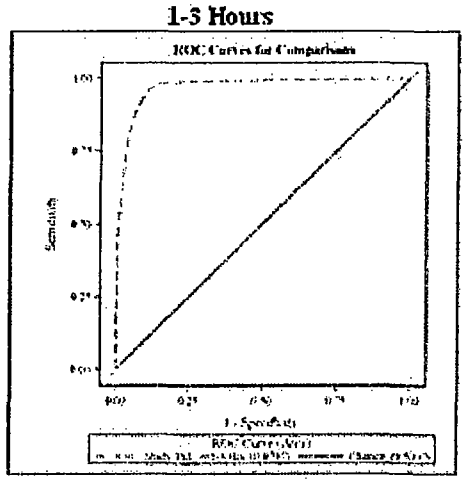
- Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) are presented below for the Admission (Baseline) draw, and for serial time intervals after admission.
- Study results show the AccuTnI assay to have significant diagnostic efficacy at all time intervals.

Hours After Admission	AUC (95% CI)	p value
Baseline	0.94 (0.92 - 0.95)	p<0.0001
1-3 Hours	0.97 (0.96 - 0.98)	p<0.0001
3-6 Hours	0.96 (0.95 - 0.98)	p<0.0001
6-9 Hours	0.94 (0.89 - 0.99)	p<0.0001

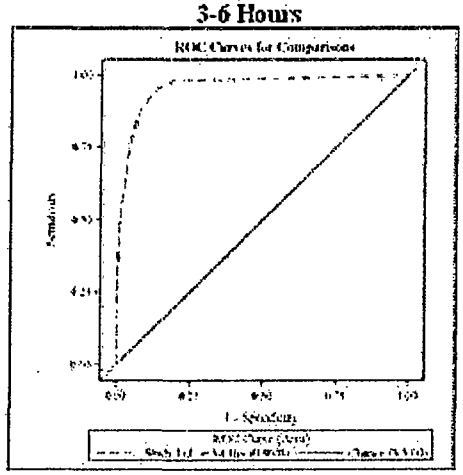
Baseline



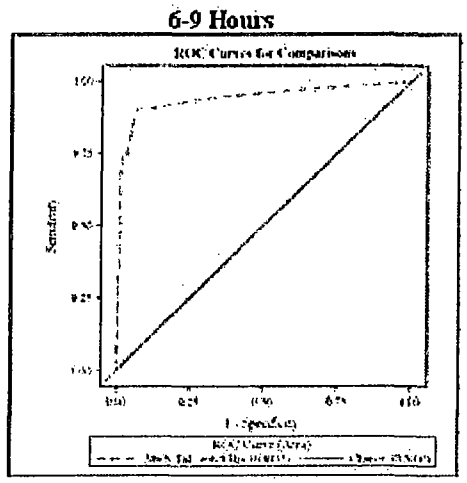
1-3 Hours



3-6 Hours



6-9 Hours



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- Sensitivity and specificity results are shown in the following tables for cutoffs between 0.02 and 0.50 ng/mL. (Note: Sample size decreases over time as patients are diagnosed, treated and/or discharged.)

Baseline						
	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	92.1	233/253	88.8 - 95.4	84.3	1412/1675	82.6 - 86.0
0.03	87.4	221/253	83.3 - 91.4	89.3	1495/1675	87.8 - 90.7
0.04	77.1	195/253	71.9 - 82.3	93.8	1572/1675	92.7 - 95.0
0.05	65.6	166/253	59.8 - 71.5	95.6	1602/1675	94.7 - 96.6
0.06	59.7	151/253	53.6 - 65.7	97.0	1625/1675	96.2 - 97.8
0.10	44.7	113/253	38.5 - 50.8	98.6	1651/1675	98.0 - 99.1
0.20	30.8	78/253	25.1 - 36.5	99.4	1665/1675	99.0 - 99.8
0.30	24.1	61/253	18.8 - 29.4	99.6	1669/1675	99.4 - 99.9
0.40	20.2	51/253	15.2 - 25.1	99.6	1669/1675	99.4 - 99.9
0.50	17.8	45/253	13.1 - 22.5	99.6	1669/1675	99.4 - 99.9

1-3 Hours						
	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	98.4	122/124	96.2 - 100.0	85.5	867/1014	83.3 - 87.7
0.03	96.0	119/124	92.5 - 99.4	89.4	907/1014	87.6 - 91.3
0.04	89.5	111/124	84.1 - 94.9	93.5	948/1014	92.0 - 95.0
0.05	80.6	100/124	73.7 - 87.6	95.8	971/1014	94.5 - 97.0
0.06	74.2	92/124	66.5 - 81.9	97.0	984/1014	96.0 - 98.1
0.10	54.0	67/124	45.3 - 62.8	98.8	1002/1014	98.2 - 99.5
0.20	42.7	53/124	34.0 - 51.4	99.4	1008/1014	98.9 - 99.9
0.30	33.1	41/124	24.8 - 41.3	99.5	1009/1014	99.1 - 99.9
0.40	28.2	35/124	20.3 - 36.1	99.6	1010/1014	99.2 - 100.0
0.50	25.0	31/124	17.4 - 32.6	99.7	1011/1014	99.4 - 100.0

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3-6 Hours						
	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	98.1	154/157	95.9 - 100.0	81.0	762/941	78.5 - 83.5
0.03	94.9	149/157	91.5 - 98.3	86.7	816/941	84.5 - 88.9
0.04	87.3	137/157	82.0 - 92.5	93.0	875/941	91.4 - 94.6
0.05	79.0	124/157	72.6 - 85.4	95.0	894/941	93.6 - 96.4
0.06	72.0	113/157	64.9 - 79.0	96.4	907/941	95.2 - 97.6
0.10	54.8	86/157	47.0 - 62.6	98.3	925/941	97.5 - 99.1
0.20	41.4	65/157	33.7 - 49.1	99.3	934/941	98.7 - 99.8
0.30	32.5	51/157	25.2 - 39.8	99.6	937/941	99.2 - 100.0
0.40	29.3	46/157	22.2 - 36.4	99.6	937/941	99.2 - 100.0
0.50	27.4	43/157	20.4 - 34.4	99.6	937/941	99.2 - 100.0

6-9 Hours						
	Sensitivity			Specificity		
TnI cutoff (≥) ng/mL	%	n/N	95% CI	%	n/N	95% CI
0.02	93.0	40/43	85.4 - 100.0	76.4	188/246	71.1 - 81.7
0.03	90.7	39/43	82.0 - 99.4	87.0	214/246	82.8 - 91.2
0.04	90.7	39/43	82.0 - 99.4	93.1	229/246	89.9 - 96.3
0.05	86.0	37/43	75.7 - 96.4	94.7	233/246	91.9 - 97.5
0.06	79.1	34/43	66.9 - 91.2	95.9	236/246	93.5 - 98.4
0.10	74.4	32/43	61.4 - 87.5	98.4	242/246	96.8 - 100.0
0.20	53.5	23/43	38.6 - 68.4	98.8	243/246	97.4 - 100.0
0.30	44.2	19/43	29.3 - 59.0	98.8	243/246	97.4 - 100.0
0.40	41.9	18/43	27.1 - 56.8	99.2	244/246	98.1 - 100.0
0.50	34.9	15/43	20.6 - 49.1	99.2	244/246	98.1 - 100.0

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9.10.4.10.2. Diagnostic Sensitivity and Specificity by Time After Admission: Summary and Conclusions

- The following table summarizes the ROC AUCs for serial time intervals after admission to the hospital.

	Hours After Admission			
	Baseline	1-3 Hours	3-6 Hours	6-9 Hours
ROC AUC	0.94	0.97	0.96	0.97

- Sensitivity and specificity results are summarized in the table on the following page.
- The cutoff determined in the Feasibility Trial (0.03 ng/mL) yielded ≥95% sensitivity for troponin measurements 1-6 hours after admission. The URL (0.02 ng/mL) yielded ≥98% sensitivity.
- Results show improved sensitivity over time from baseline to 1-6 hours as expected based upon troponin kinetics: literature reports have shown that cardiac troponin begins to rise 3-4 hours after the onset of myocardial injury. Sensitivity was slightly lower at 6-9 hours after admission, reflecting current guidelines for rapid diagnosis/treatment of MI, and the subsequent removal of subjects receiving timely reperfusion therapy (post-intervention TnI) from the study population.
- The cutoff determined in the Feasibility Trial (0.03 ng/mL) yielded 87-89% specificity. The URL (0.02 ng/mL) yielded 76% to 86% specificity.
- In clinical practice, even higher specificity is attained from detection of a rise and/or fall in marker values as described in the Universal Definition of MI. When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.

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Cutoff	Hours After Admission	Sensitivity	Specificity
0.02 ng/mL	Baseline	92%	84%
	1-3 Hours	98%	86%
	3-6 Hours	98%	81%
	6-9 Hours	93%	76%
0.03 ng/mL	Baseline	87%	89%
	1-3 Hours	96%	89%
	3-6 Hours	95%	87%
	6-9 Hours	91%	87%

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9.10.4.11. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

- CLSI Guideline I/LA21-A2 "Clinical Evaluation of Immunoassays" states:
  - "Once particular decision thresholds are identified by the ROC analysis, performance characteristics such as positive and negative predictive value may be useful."
  - "PV analysis, unlike ROC analysis, is prevalence-dependent."
  - "ROC describes how well the test discriminates between two categories of subjects, while PV describes the probable meaning of normal or abnormal results once the cutoff and prevalence are defined."
- Therefore, Positive Predictive Values (PPV) and Negative Predictive Values (NPV) were calculated, and results are shown in the following tables for defined cutoffs of 0.03 ng/mL (ROC cutoff) and 0.02 ng/mL (URL).

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9.10.4.11.1. PPV and NPV Results by Time After Symptom Onset

- PPV and NPV are shown in the following tables for samples drawn <8 hours and ≥8 hours after symptom onset.
  - NPV: Nearly 100% of patients with TnI <0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI).
  - PPV: Approximately 50% of patients with TnI ≥0.03 ng/mL were diagnosed with MI. The ROC cutoff (0.03) performed substantially better than the URL (0.02).

Results for ROC Cutoff (0.03 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Symptom Onset	PPV (95% CI)	n/N	NPV (95% CI)	n/N
< 8 hours	58.3 (52.3 - 64.3)	151/259	98.4 (97.6 - 99.3)	885/899
≥ 8 hours	50.5 (44.8 - 56.2)	150/297	99.1 (98.5 - 99.7)	966/975

Results for URL (0.02 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Symptom Onset	PPV (95% CI)	n/N	NPV (95% CI)	n/N
< 8 hours	48.8 (43.3 - 54.2)	159/326	99.3 (98.7 - 99.9)	826/832
≥ 8 hours	43.0 (37.9 - 48.1)	154/358	99.5 (99.0 - 99.9)	909/914

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9.10.4.11.2. PPV and NPV Results by Time After Admission

- PPV and NPV are presented in the following tables for serial time intervals after admission.
  - NPV: Nearly 100% of patients with TnI <0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI).
  - PPV: Approximately 55% of patients with TnI ≥0.03 ng/mL were diagnosed with MI. The ROC cutoff (0.03) performed substantially better than the URL (0.02).

Results for ROC Cutoff (0.03 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Admission	PPV (95% CI)	n/N	NPV (95% CI)	n/N
Baseline	55.1 (50.2 - 60.0)	221/401	97.9 (97.2 - 98.6)	1495/1527
1-3 hours	52.7 (46.1 - 59.2)	119/226	99.5 (99.0 - 99.9)	907/912
3-6 hours	54.4 (48.5 - 60.3)	149/274	99.0 (98.4 - 99.7)	816/824
6-9 hours	54.9 (43.4 - 66.5)	39/71	98.2 (96.4 - 99.9)	214/218

Results for URL (0.02 ng/mL)				
	Positive Predictive Value (%)		Negative Predictive Value (%)	
Time After Admission	PPV (95% CI)	n/N	NPV (95% CI)	n/N
Baseline	47.0 (42.6 - 51.4)	233/496	98.6 (98.0 - 99.2)	1412/1432
1-3 hours	45.4 (39.4 - 51.3)	122/269	99.8 (99.5 - 100.0)	867/869
3-6 hours	46.2 (40.9 - 51.6)	154/333	99.6 (99.2 - 100.0)	762/765
6-9 hours	40.8 (31.1 - 50.5)	40/98	98.4 (96.7 - 100.0)	188/191

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9.10.4.11.3. PPV and NPV: Summary and Conclusions

- NPV (probability of non-MI diagnosis in patients with non-elevated TnI) approached 100% in this study.
- PPV (probability of MI diagnosis in patients with elevated TnI) is directly proportional to the incidence of disease in the intended use population.
- The overall MI incidence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Reports in the literature have shown that non-representative study populations with high MI incidence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPV's (up to 80-90%) (Jaffe AS. Clin Chem. 2010;56:342-344) (Reichlin T. N Engl J Med. 2009;361:858-867) (Keller T. N Engl J Med. 2009;361:868-877).
- The current study produced PPV's of approximately 50-55% despite the expected low incidence of MI observed in the ED (13%). These same results were obtained with the Siemens ADVIA Centaur TnI-Ultra assay as shown in the "Method Comparison To Predicate" section of this submission. These PPV's are representative of troponin itself and the use of low cutoffs, emphasizing the importance of serial samples when low cutoffs are used. Nevertheless, even a single elevated troponin value increases the "risk" of MI from 13% to ~50-55%, providing important information to the clinician.
- As CLSI Guideline I/LA21-A2 "Clinical Evaluation of Immunoassays" states, "PV analysis, unlike ROC analysis, is prevalence-dependent." Therefore, variations in region-to-region and facility-to-facility MI incidence make PPV logistically difficult to interpret and implement for uniform use

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in patient management. Shifting prevalence over time also affects PV as MI's are treated and removed from the diagnostic population.

- In clinical practice, the use of a defined cutoff from ROC analysis (95% sensitivity, unaffected by prevalence), detection of a rise and/or fall in serial marker values as specified by the Universal Definition of MI, and interpretation of test results in the clinical context of each patient, allow acute events such as MI to be distinguished from other conditions causing myocardial injury.

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9.10.4.12. Non-MI Patients with Elevated TnI Values (Myocardial Damage)

- Extensive demographic data, cardiovascular risk factors, pre-existing conditions, comorbidities, medications, concomitant complications during hospitalization, and diagnoses were obtained for all subjects enrolled in the study in order to fully describe and characterize the study population.
- The detailed medical histories obtained in this trial allowed for a complete analysis of Non-MI patients with elevated TnI values, in order to ascertain potential causes of myocardial injury.

9.10.4.12.1. Results

- Of the 1,676 Non-MI patients, 217 (13%) had at least one TnI value greater than or equal to the cutoff (0.03 ng/mL) on one or more of the serial draws.
- Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure, pulmonary embolism, or diabetes that may result in myocardial damage, as shown in the following table.

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Reasons for Elevated Troponin Values in Non-MI Patients	n/217 (%)
Stable angina	11 (5.1)
Unstable angina	20 (9.2)
Atrial fibrillation / flutter	34 (15.7)
COPD or Asthma	28 (12.9)
Cancer	14 (6.5)
Cardiomyopathy	9 (4.1)
Cardiotoxic Drugs	14 (6.5)
Carditis	2 (0.9)
Chronic Kidney Disease or Renal Failure	73 (33.6)
Cirrhosis	2 (0.9)
Coronary Artery Disease (CAD)	108 (49.8)
Deep Vein Thrombosis	5 (2.3)
Diabetes Mellitus	90 (41.5)
Dyslipidemia or Hypercholesterolemia	128 (59.0)
Heart Failure	111 (51.2)
Hypertension (HTN)	179 (82.5)
Infection (e.g. HIV, Hepatitis, Sepsis, etc.)	28 (12.9)
Pacemaker / Defibrillator (ICD)	10 (4.6)
Peripheral Vascular Disease (PVD) or Peripheral Artery Disease (PAD)	19 (8.8)
Prior Acute Myocardial Infarction (AMI)	83 (38.2)
Prior Coronary Artery Bypass Graft (CABG)	43 (19.8)
Prior Coronary Artery Stent or Angioplasty	65 (30.0)
Prior Stroke or Cerebral Vascular Accident	31 (14.3)
Pulmonary Embolism	10 (4.6)
Stroke	5 (2.3)
Tachycardia	12 (5.5)
Other Cardiac Condition	21 (9.7)

Note: Total number of subjects and percentages may not add to 100% because patients may have more than one condition.

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9.10.4.12.2. Non-MI Patients with Elevated TnI Values (Myocardial Damage): Summary and Conclusions

- 13% of non-MI patients had at least one TnI value greater than or equal to the cutoff (0.03 ng/mL) on one or more of the serial draws.
- 98.6% of these patients were found to have cardiac conditions such as unstable or stable angina, atrial or ventricular fibrillation, tachycardia, cardiomyopathy, carditis, acute exacerbation of heart failure, hypertensive emergency, severe coronary artery disease; or non-cardiac conditions such as renal failure, pulmonary embolism, or diabetes that may result in myocardial damage. 17% (36/217) of the patients underwent catheterization, and nearly half (44%, 16/36) of these had one or more arteries with >50% occlusion. 17 patients required angioplasty, stent placement, coronary artery bypass graft surgery (CABG), or other percutaneous coronary intervention (PCI) due to advanced arterial stenosis or occlusion.
- Results are consistent with literature findings that TnI may be elevated in coronary and non-coronary disease in the presence of myocardial injury (Agewall et al. Eur Heart J 2011;32:404-411) (Kelley et al. Clin Chem 2009;55:2098-2122).
- Study results suggest that an elevated TnI value in a non-MI patient should not be disregarded as unimportant. Troponin is specific for myocardial injury and has clinical utility in identifying patients with acute and chronic cardiac damage. When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury (Universal Definition of MI: Thygesen K. Circulation 2007;116:2634-53).

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9.10.5. Pivotal Efficacy Trial: Summary and Conclusions

- A prospective multicenter Pivotal Trial was designed and conducted based on the scientific literature and cardiology guidelines, the prospective Feasibility Trial, the FDA Document "Points to Consider for Troponin pre-IDE and 510(k) submissions" (April 30, 2010), and pre-IDE discussions with FDA.
- A total of 1,929 patients with serial samples were evaluated in this Pivotal Trial.
- Significant diagnostic efficacy was demonstrated in both Feasibility Trial and Pivotal Trial at all time intervals after ED admission and at all time intervals after symptom onset.
- The Feasibility Trial ROC curve analysis determined that a cutoff of 0.03 ng/mL (95% CI 0.01 - 0.04) yielded 95% sensitivity. This cutoff was validated by the larger multicenter Pivotal Trial: A cutoff of 0.03 ng/mL yielded 94% (91-98%) sensitivity. This 0.03 ng/mL cutoff is within the 95% Confidence Interval of results from the Feasibility Trial.

AccuTnI Cutoffs Yielding 95% Sensitivity

Feasibility Trial (hypothesized 95% CI cutoff range)	Pivotal Trial
0.03 (0.01 - 0.04) ng/mL	0.03 ng/mL

- Therefore, the Pivotal Trial results are in agreement with the Feasibility Trial results, and both trials have demonstrated significant diagnostic efficacy for the AccuTnI assay.
- The AccuTnI assay is intended for use as an aid in the diagnosis of myocardial infarction. A cutoff of 0.03 ng/mL is recommended.
- The AccuTnI assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial

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injury (Universal Definition of MI: Thygesen K. Circulation 2007;116:2634-53).

- The greater diagnostic sensitivity of later generation troponin assays with lower cutoffs as recommended by consensus cardiology guidelines allows for the opportunity to rapidly initiate effective medical management.

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9.11. Method Comparison to Predicate

9.11.1. Study Objectives

- To further demonstrate substantial equivalence of the AccuTnI Assay to the predicate device Siemens ADVIA Centaur TnI-Ultra Assay, the following analyses were performed using native patient samples from the intended use population with troponin values in the clinically relevant range:
  - Regression analysis and correlation coefficient
  - Concordance (% agreement)
  - Diagnostic Sensitivity and Specificity
  - Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

9.11.2. Study Sites / Investigators

- A total of 14 geographically diverse sites participated. These are the same sites that participated in the Pivotal Efficacy Trial.

9.11.3. Study Design

9.11.3.1. Subject Inclusion and Exclusion Criteria

- This study contains samples from the subjects enrolled in the Pivotal Efficacy Trial.
- Only samples with test results for both AccuTnI and TnI-Ultra assays were included.

9.11.3.2. Sample Size Rationale and Statistical Analysis Methods

- In the "CLSI Guideline EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition", a minimum of 100 specimens is recommended for a manufacturer method comparison analysis. More samples improve confidence in the statistical estimates.

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- Passing-Bablok regression analysis was performed to determine slope and intercept. Pearson's correlation coefficient (r) was calculated to assess the strength of the relationship between the methods.
- To evaluate the clinical concordance of the two methods, the concordant and discordant proportions were calculated to assess agreement.

9.11.3.3. Specimen Testing Methods

- AccuTnI results were determined on the Access 2 Instrument in singlet on 3 lots of reagent.
- TnI-Ultra results were determined on the Siemens ADVIA Centaur Instrument in singlet on 4 lots of reagent.
- Testing was performed by four external laboratory testing sites (Sites #1, 3, 4, 5, listed in the Attachment entitled "Specimen Testing Sites").

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9.11.4. Results

9.11.4.1. Number of Samples

- The number of samples in these analyses against the reference method are shown in the following table. All samples were tested with both AccuTnI and TnI-Ultra assays.
  - The "Regression Analysis and Correlation Coefficient" analysis includes only samples within the reportable range of the predicate assay (0.01 to 50 ng/mL).
  - The "Concordance (% agreement)" analysis includes all samples.
  - The "Diagnostic Sensitivity and Specificity" ROC analysis and the "Positive Predictive Value (PPV) and Negative Predictive Value (NPV)" analysis include one sample per subject, drawn ≥8 hours after symptom onset.

	Number of Samples
MI	611
Non-MI	3,986
Total	4,597

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9.11.4.2. Regression Analysis and Correlation Coefficient

- The majority of the samples in this study of the intended use population are in the clinically important low end of the assay range: 99% of the samples were ≤5 ng/mL.
- Results from the regression and correlation analyses comparing the AccuTnI and TnI-Ultra assays are presented in the following table for:
  - Samples within the reportable range of the predicate assay (0.01 to 50 ng/mL)
  - Samples within the clinically important low end of the assay (0.01 to 5 ng/mL)
- Excellent correlation between methods was observed (r = 0.98). These results further demonstrate substantial equivalence of the AccuTnI Assay to the predicate device Siemens ADVIA Centaur TnI-Ultra Assay.

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.01 - 50	1,717	0.68 (0.67 - 0.69)	0.00 (0.00 - 0.00)	r = 0.98
0.01 - 5	1,664	0.70 (0.70 - 0.71)	0.00 (0.00 - 0.00)	r = 0.98

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9.11.4.3. Concordance (% agreement)

- Concordance (percent agreement) with the AccuTnI and TnI-Ultra assays was evaluated, using MI cutoffs of 0.03 and 0.04 ng/mL respectively.
- The TnI-Ultra cutoff of 0.04 ng/mL used in this analysis is the predicate manufacturer's claimed package insert cutoff for diagnosis of MI based on the ESC/ACC/AHA/WHF consensus cardiology guidelines. The insert states: "The overall 99th percentile for the ADVIA Centaur TnI-Ultra assay is 0.04 ng/mL. The potential range of results for the 99th percentile is 0.02 to 0.06 ng/mL for the ADVIA Centaur family of systems, dependent upon sample type, instrument, and reagent lot."
- A total of 4,597 samples are included in this analysis.
- Excellent agreement between methods was observed: 93% (4294/4597).

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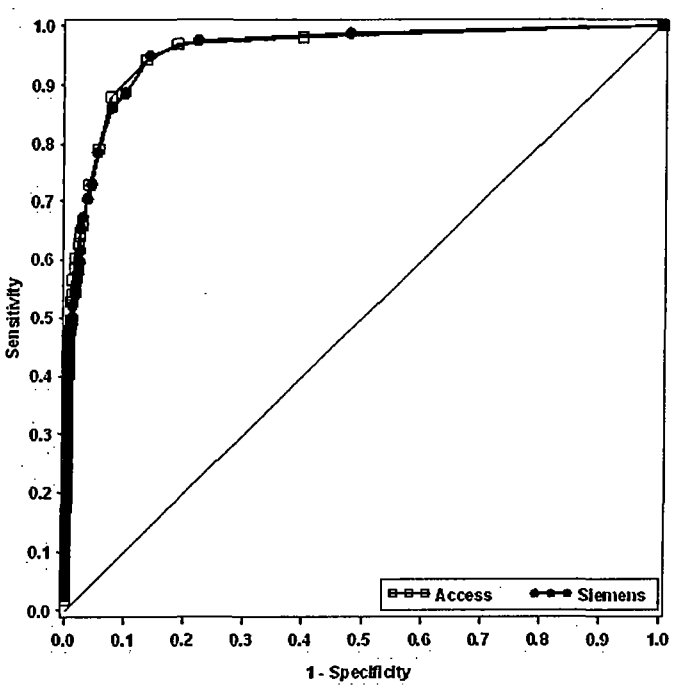
9.11.4.4. Diagnostic Sensitivity and Specificity

- In addition to the concordance analysis shown in the previous section, another method to compare clinical performance, ROC curve analysis, is shown below for the AccuTnI and TnI-Ultra assays.
- Diagnostic sensitivity and specificity are presented in a table following the ROC curve.
- A total of 1271 subjects (159 MI, 1112 Non-MI) are included in this analysis, using one sample per subject, drawn ≥8 hours after symptom onset.
- Significant diagnostic efficacy was observed for both assays:
  - AccuTnI AUC = 0.96 (95% CI: 0.94 - 0.98), p<0.0001
  - TnI-Ultra AUC = 0.96 (95% CI: 0.94 - 0.98), p<0.0001
- The AUCs were not statistically different for the two assays (p = 0.97).



- Substantially equivalent sensitivity and specificity results to the predicate device were obtained, as shown in the following table.

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Cutoff (ng/mL)	Assay	Sensitivity			Specificity		
		%	n / N	95% CI	%	n / N	95% CI
0.03	AccuTnI	94.3	150/159	90.7-97.9	86.8	966/1113	84.8-88.8
	TnI-Ultra	95.0	151/159	91.6-98.4	86.3	960/1112	84.3-88.3
0.04	AccuTnI	88.1	140/159	83.0-93.1	92.7	1032/1113	91.2-94.2
	TnI-Ultra	88.7	141/159	83.8-93.6	90.4	1005/1112	88.6-92.1

- The TnI-Ultra cutoff of 0.04 ng/mL is the predicate manufacturer's claimed package insert cutoff for diagnosis of MI based on the ESC/ACC/AHA/WHF consensus cardiology guidelines. The TnI-Ultra package insert states: "The overall 99th percentile for the ADVIA Centaur TnI-Ultra assay is 0.04 ng/mL. The potential range of results for the 99th percentile is 0.02 to 0.06 ng/mL for the ADVIA Centaur family of systems, dependent upon sample type, instrument, and reagent lot."
- For comparison purposes to cleared clinical performance characteristics of the predicate device, diagnostic sensitivity and specificity for the TnI-Ultra assay are not provided in the insert for a cutoff of 0.04 ng/mL. However, the insert states the TnI-Ultra diagnostic sensitivity is 97.3% (92.4 - 99.4) for a cutoff of 0.78 ng/mL using the historical WHO definition of MI. Current study findings show similar diagnostic sensitivity using contemporary ESC/ACC/AHA/WHF consensus guidelines that recommend lower cutoffs and use the updated universal definition of MI.
- These results further demonstrate substantial equivalence of the AccuTnI Assay to the predicate device Siemens ADVIA Centaur TnI-Ultra Assay, and support the intended use as an aid in the diagnosis of myocardial infarction using contemporary ESC/ACC/AHA/WHF consensus guidelines.

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9.11.4.5. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

- Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are shown in the table on the following page for the AccuTnI and TnI-Ultra assays.
- A total of 1271 subjects (159 MI, 1112 Non-MI) are included in this analysis, using one sample per subject, drawn ≥8 hours after symptom onset.
- Substantially equivalent results to the predicate device were obtained using contemporary ESC/ACC/AHA/WHF consensus guidelines recommending lower cutoffs and the Universal Definition of MI.
    - NPV's (probability of non-MI diagnosis in patients with non-elevated TnI) approached 100%.
    - PPV's (probability of MI in patients with elevated TnI) of approximately 50-60% are observed despite the expected low incidence of MI observed in the ED (13%). These PPV's are representative of troponin itself and the use of low cutoffs. Nevertheless, an elevated TnI result increases the "risk" of MI from 13% to ~50-60%, providing important information to the clinician.
- Values in the table do not reflect serial blood draws as would be obtained in clinical practice. Detection of a rise and/or fall in serial marker values as specified by the Universal Definition of MI, and interpretation of test results in the clinical context of each patient, allow acute events such as MI to be distinguished from other conditions causing myocardial injury.
- These results further demonstrate substantial equivalence of the AccuTnI Assay to the predicate device Siemens ADVIA Centaur TnI-Ultra Assay.

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Cutoff (ng/mL)	Assay	Positive Predictive Value (%)		Negative Predictive Value (%)	
		PPV (95% CI)	n/N	NPV (95% CI)	n/N
0.03	AccuTnI	50.5 (44.8 - 56.2)	150/297	99.1 (98.5 - 99.7)	966/975
	TnI-Ultra	49.8 (44.2 - 55.5)	151/303	99.2 (98.6 - 99.7)	960/968
0.04	AccuTnI	63.3 (57.0 - 69.7)	140/221	98.2 (97.4 - 99.0)	1032/1051
	TnI-Ultra	56.9 (50.7 - 63.0)	141/248	98.2 (97.4 - 99.0)	1005/1023

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9.11.5. Method Comparison to Predicate: Summary and Conclusions

To further demonstrate substantial equivalence of the AccuTnI Assay to the predicate device Siemens ADVIA Centaur TnI-Ultra Assay, the following analyses were performed: Regression/Correlation, Concordance, Sensitivity/Specificity, and PPV/NPV.

Regression, correlation: Excellent correlation between methods was observed (r=0.98).

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.01 - 50	1,717	0.68 (0.67 - 0.69)	0.00 (0.00 - 0.00)	r = 0.98
0.01 - 5	1,664	0.70 (0.70 - 0.71)	0.00 (0.00 - 0.00)	r = 0.98

Concordance (% agreement): The AccuTnI assay provides high concordant rates with the predicate TnI-Ultra assay, using MI cutoffs of 0.03 and 0.04 ng/mL respectively. A total of 4,597 samples were included in this analysis. Excellent agreement between methods was observed: 93% (4294/4597).

Diagnostic Sensitivity and Specificity: Significant diagnostic efficacy was observed with ROC curve analyses for both assays (AccuTnI AUC=0.96; TnI-Ultra AUC=0.96). The AUCs were not statistically different (p = 0.97). Substantially equivalent sensitivity and specificity results to the predicate device were obtained, as shown in the following table.

Cutoff (ng/mL)	Assay	Sensitivity			Specificity		
		%	n / N	95% CI	%	n / N	95% CI
0.03	AccuTnI	94.3	150/159	90.7-97.9	86.8	966/1113	84.8-88.8
	TnI-Ultra	95.0	151/159	91.6-98.4	86.3	960/1112	84.3-88.3
0.04	AccuTnI	88.1	140/159	83.0-93.1	92.7	1032/1113	91.2-94.2
	TnI-Ultra	88.7	141/159	83.8-93.6	90.4	1005/1112	88.6-92.1

Positive Predictive Value (PPV) and Negative Predictive Value (NPV): Substantially equivalent results to the predicate device were obtained using contemporary ESC/ACC/AHA/WHF consensus guidelines recommending lower cutoffs and the Universal Definition of MI.

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Cutoff (ng/mL)	Assay	Positive Predictive Value (%)		Negative Predictive Value (%)	
		PPV (95% CI)	n/N	NPV (95% CI)	n/N
0.03	AccuTnI	50.5 (44.8 - 56.2)	150/297	99.1 (98.5 - 99.7)	966/975
	TnI-Ultra	49.8 (44.2 - 55.5)	151/303	99.2 (98.6 - 99.7)	960/968
0.04	AccuTnI	63.3 (57.0 - 69.7)	140/221	98.2 (97.4 - 99.0)	1032/1051
	TnI-Ultra	56.9 (50.7 - 63.0)	141/248	98.2 (97.4 - 99.0)	1005/1023

Conclusions: To compare the AccuTnI Assay to the predicate device Siemens ADVIA Centaur TnI-Ultra Assay, the following analyses were performed using native patient samples from the intended use population with troponin values in the clinically relevant range: Regression/Correlation, Concordance, Sensitivity/Specificity, and PPV/NPV. Study results demonstrated substantial equivalence of the AccuTnI assay to the predicate device Siemens ADVIA Centaur TnI-Ultra assay. Results support the intended use, and demonstrate that the AccuTnI assay may be used as an aid in the diagnosis of myocardial infarction.

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9.12. SAMPLE MATRIX COMPARISON (Lithium Heparin Plasma, Serum)

9.12.1. Study Objectives

- To compare lithium heparin plasma and serum using native patient samples from the intended use population with troponin values in the clinically relevant range

9.12.2. Study Sites / Investigators

- A total of 14 geographically diverse sites participated. These are the same sites that participated in the Pivotal Efficacy Trial.

9.12.3. Study Design

9.12.3.1. Subject Inclusion and Exclusion Criteria

- This study contains samples from the subjects enrolled in the Pivotal Efficacy Trial.
- Lithium heparin plasma and serum matched sample sets were collected at each blood draw from each patient.
- Matched sample sets were included in this Matrix Comparison study. One set of matched samples from each subject was used. Samples below the limit of detection or above the reportable range were not included in the analysis.
- Matched sample sets were randomly selected, based on TnI level, from among the entire pivotal trial cohort in order to span the range of TnI levels observed in the pivotal trial.

9.12.3.2. Sample Size Rationale and Statistical Analysis Methods

- In the "CLSI Guideline EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition", a minimum of 100 specimens is recommended for a manufacturer method comparison analysis. Matrix comparison studies commonly include up to 50 matched sample sets; however, more samples improve confidence in the statistical estimates.

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- Passing-Bablok regression analysis was performed to determine slope and intercept. Pearson's correlation coefficient (r) was calculated to assess the strength of the relationship between sample types.

9.12.3.3. Specimen Testing Methods

- Lithium heparin plasma and serum results were determined on the Access 2 Instrument in singlet, using 3 lots of reagent.
- Matched sample sets were tested on the same day within the same run.
- Testing was performed by three external laboratory sites (Sites #1, 3, and 4, listed in the Attachment entitled "Specimen Testing Sites").

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9.12.4. Results

9.12.4.1. Number of Samples

- A total of 107 matched samples were included in this analysis. One set of matched samples from any specific subject was used, so the number of subjects (n=107) and samples were the same.

9.12.4.2. Regression Analysis and Correlation Coefficient

- Results from the regression and correlation analyses comparing lithium heparin plasma and serum are presented in the following table for:
  - Samples from 0.01 to 20 ng/mL
  - Samples within the clinically important low end of the assay (0.01 to 5 ng/mL)
- Excellent agreement between sample types was observed.

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.01 - 20	107	1.00 (0.98 - 1.00)	0.00 (0.00 - 0.00)	r = 1.00
0.01 - 5	104	1.00 (1.00 - 1.00)	0.00 (0.00 - 0.00)	r = 1.00

- These results are similar to those reported in the Analytical Performance section of this submission (Matrix Comparison Study).

9.12.5. Sample Matrix Comparison: Summary and Conclusions

- Results from the regression and correlation analyses comparing lithium heparin plasma and serum showed excellent agreement between sample types in the intended use population.
- Results support the intended use, and demonstrate that the AccuTnI assay may be used for the quantitative determination of cardiac TnI levels in human serum and plasma to aid in the diagnosis of myocardial infarction.

Questions? Contact FDA/CDRH/OSE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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9.13. Attachment I: Bibliography

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Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J. 2010;31:2197-2204.

FDA document: Points to Consider for Troponin pre-IDE and 510(k) submissions (April 30, 2010)

CLSI Guideline C28-A3c: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition

CLSI Guideline EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Addition

CLSI Guideline EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition

CLSI Guideline EP14-A2: Evaluation of Matrix Effects; Approved Guideline - Second Addition

CLSI Guideline EP24-A2: Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Draft Guideline - Second Edition

CLSI Guideline I/LA21-A2: Clinical Evaluation of Immunoassays; Approved Guideline - Second Edition

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9.14. Attachment II: Investigational Sites (Subject Enrollment)

REFERENCE INTERVAL TRIAL

Site #	Database Site ID	Principal Investigator, Site
A	sd	Kurtis R. Bray, PhD Clinical Research Department Beckman Coulter, Inc. 2470 Faraday Avenue Carlsbad, CA 92010 760-438-6570 krbray@beckman.com
B	ar	William L. Roberts, MD, PhD Medical Director, Automated Core Laboratory ARUP Laboratories 500 Chipeta Way Salt Lake City, UT 84108 800-242-2787 william.roberts@aruplab.com
C	bc	Mr. Sixto F. Pacheco President and CEO BioCollections Worldwide, Inc. 7180 N.E. 2nd Avenue Miami, FL 33138 305-792-2090 sixto.pacheco@biocollections.com
D	jt	Denise L. Geiger, PhD, MT (ASCP), DLM (ASCP) Director of Laboratories, Clinical Chemist John T. Mather Memorial Hospital 75 North Country Road Port Jefferson, NY 11777 631-473-1320 ext 4137 dgeiger@matherhospital.org
E	pn	Alice C. Shapiro, PhD, RD, LN Clinical Principal Investigator Park Nicollet Institute 3800 Park Nicollet Blvd. Minneapolis, MN 55416 952-993-1704 alice.shapiro@ParkNicollet.com
F	ch	Cheryl Hodges-Savola, PhD Clinical Research Department Beckman Coulter, Inc. 1000 Lake Hazeltine Drive Chaska, MN 55318 952-368-7851 cahodgessavola@beckman.com
G	rr	Karen E. Kam, MD, CPI Certified Physician Investigator Ridgeview Research Ridgeview Chaska Medical Plaza 3000 Hundertmark Road Chaska, MN 55318 952-556-2686 karen.kam@ridgeviewmedical.org

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FEASIBILITY EFFICACY TRIAL

Site #	Principal Investigator, Site
1	Jin Ho Han, MD, MSc Department of Emergency Medicine Vanderbilt University Medical Center 703 Oxford House 1313 21st Ave South Nashville, TN 37232 615-936-0093 jin.h.han@vanderbilt.edu

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PIVOTAL EFFICACY TRIAL

Site #	Principal Investigator, Site
1	Jon W. Schrock, MD, FACEP, FAHA Director Clinical Decision Unit, Department of Emergency Medicine Case Western Reserve School of Medicine MetroHealth Medical Center 2500 MetroHealth Drive, BG 372 Cleveland, OH 44109 216-778-5747 or 3444 jschrock@metrohealth.org
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4	Deborah B. Diercks, MD, MSc Professor, Department of Emergency Medicine UC Davis Health System 2315 Stockton Blvd Sacramento, CA 95817 916-734-4052 dbdiercks@ucdavis.edu
6	Alan B. Storrow, MD Associate Professor, Department of Emergency Medicine Vanderbilt University Medical Center 703 Oxford House 1313 21st Ave South Nashville, TN 37232 615-936-5934 or 8379 or 4490 alan.b.storrow@vanderbilt.edu
7	Richard M. Nowak, MD, MBA Department of Emergency Medicine Henry Ford Health System 2799 West Grand Boulevard Detroit, MI 48202 313-916-1557 rnowak1@hfhs.org
8	Erik B. Kulstad, MD, MS Research Director, Department of Emergency Medicine Advocate Christ Medical Center 4440 West 95th Street Oak Lawn, IL 60453 708-684-3889 ekulstad@gmail.com kulstad@uic.edu
9	Daniel P. Zelinski, MD, PhD Assistant Professor, Department of Emergency Medicine The Ohio State University Medical Center 4510 Cramblett Hall 456 W. 10th Avenue Columbus, OH 43210 614-293-4027 daniel.zelinski@osumc.edu

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10	Frank LoVecchio, DO, MPH, FACEP Research Director, Department of Emergency Medicine Maricopa Medical Center 2601 East Roosevelt Street Phoenix, AZ 85008 602-999-9729 frank.lovecchio@bannerhealth.com
11	Adam J. Singer, MD Professor and Vice-Chair for Research Department of Emergency Medicine State University of New York (SUNY) at Stony Brook Health Science Center Level-3 Room 061 Stony Brook, NY 11794-8350 631-444-7857 adam.singer@stonybrook.edu
12	Christopher J. Hogan, MD Department of Emergency Medicine Virginia Commonwealth University (VCU) Medical Center Main Hospital, Room G107 1250 E. Marshall Street Richmond, VA 23298-0401 804-828-6047 chogan@mcvh-vcu.edu
13	Gary F. Headden, MD Medical Director, Chest Pain Center Division of Emergency Medicine Medical University of South Carolina (MUSC) 169 Ashley Avenue, MSC 300 Charleston, SC 29425 843-792-9705 headdeng@musc.edu
14	Christian Fromm, MD, FAAEM, FACEP Department of Emergency Medicine Maimonides Medical Center 965 48th Street, 2nd Floor Brooklyn, NY 11219 718-283-6391 cfromm@maimonidesmed.org
15	Marna R. Greenberg, DO, MPH Department of Emergency Medicine Lehigh Valley Hospital 1240 S. Cedar Crest Blvd., Suite 212 Allentown, PA 18103 610-402-7168 marna.greenberg@lvh.com
16	Tracie I. Shea, MD Department of Emergency Medicine Covenant Medical Center 1447 North Harrison Saginaw, MI 48602 402-850-7764 toushea77@hotmail.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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9.15. Attachment III : Specimen Testing Sites (Laboratories)

SPECIMEN TESTING SITES (Laboratories)

Site #	Principal Investigator, Site
1	William L. Roberts, MD, PhD Medical Director, Automated Core Laboratory ARUP Laboratories 500 Chipeta Way Salt Lake City, UT 84108 800-242-2787 Ext. 2086 801-583-2787 Ext. 2086 William.Roberts@aruplab.com
2	Cabrini Delaney Manager, Clinical Trials Division Quest Diagnostics / Specialty Laboratories 27027 Tourney Road Valencia, CA 91355 1-800-944-7271 Ext. 6519 661-799-6519 661-799-6063 CDelaney@specialtylabs.com
3	Robert H. Christenson, PhD, DABCC, FACB Director, Clinical Chemistry Laboratories Professor of Pathology and Medical and Research Technology University of Maryland Medical Center 22 S. Greene Street Baltimore, MD 21201 410-328-8672 RChristenson@umm.edu
4	Deborah H. Sun, PhD Scientific Director of Clinical Pathology South Bend Medical Foundation 530 N. Lafayette Blvd. South Bend, IN 46601 574-234-4176 Ext. 1245 dsun@sbmf.org
5	James C. Ritchie, PhD, DABCC, FACB Emory University, Emory University Hospital Department of Pathology and Laboratory Medicine 1364 Clifton Road NE, Room F147B Atlanta, GA 30322 404-712-7178 jritchi@emory.edu

Questions? Contact FDA/CDRH/OSE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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9.16. Attachment IV: Independent Central Adjudication Panel Members

INDEPENDENT CENTRAL ADJUDICATION PANEL MEMBERS

Adj #	Adjudicator
A	Christopher deFilippi, MD University of Maryland School of Medicine Division of Cardiology 22 S. Greene Street, Room S-3B08 Baltimore, MD 21201-1559 410-328-7204 410-908-5858 cdefilip@medicine.umaryland.edu
B	Gautam V. Ramani, MD University of Maryland School of Medicine Division of Cardiology 22 S. Greene Street, Room S-3B08 Baltimore, MD 21201-1559 410-328-2613 GRamani@medicine.umaryland.edu
C	Robert P. Giugliano, MD, SM Brigham and Women's Hospital, Harvard Medical School TIMI Study Group / Cardiovascular Division 350 Longwood Avenue, 1st Floor Boston, MA 02115 617-278-0145 RGiugliano@partners.org
D	Christian T. Ruff, MD Brigham and Women's Hospital, Harvard Medical School TIMI Study Group / Cardiovascular Division 350 Longwood Avenue, 1st Floor Boston, MA 02115 617-278-0145 CRuff@partners.org

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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9.17. Attachment V: Form FDA 3454 "Certification: Financial Interest and Arrangements of Clinical Investigators"

See signed FORMS FDA 3454 on the following pages.

- Reference Interval Trial
- Feasibility Efficacy Trial
- Pivotal Efficacy Trial
- Specimen Testing Laboratories
- Independent Central Adjudication Panel

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Form FDA 3454: Reference Interval Trial

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No [illegible]
Expiration Date: August 31, 2012

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

[X] (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See Attached List (Reference Interval Trial)	
DL Geiger, JT Mather Hosp, See attached Form1455	

[ ] (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

[ ] (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Cheryl Hodges-Savola, PhD	Senior Manager, Clinical Studies
FIRM/ORGANIZATION: Beckman Coulter, Inc.	
SIGNATURE	DATE (mm/dd/yyyy): 04/09/2012

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

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Rockville, MD 20850

FORM FDA 3454 (12/09)

Reference Interval Trial Enrollment Sites

Site	Principal Investigator	Institution
A	Kurtis R. Bray, PhD	Beckman Coulter, Carlsbad, CA
B	William L. Roberts, MD, PhD	ARUP Laboratories
C	Sixto F. Pacheco	BioCollections Worldwide, Inc.
D	Denise L. Geiger, PhD, MT (ASCP), DLM	John T. Mather Memorial Hospital
E	Alice C. Shapiro, PhD, RD, LN	Park Nicollet Institute
F	Cheryl Hodges-Savola, PhD	Beckman Coulter, Chaska, MN
G	Karen E. Karn, MD, CPI	Ridgeview Research

Questions? Contact FDAVCDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Form FDA 3455: Reference Interval Trial

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Denise L. Geiger, Ph.D. (name of clinical investigator), who participated as a clinical investigator in the submitted study Reference Interval Study for Access II Immunoassay AccuTnI (name of test) Assay Protocol #: TnI-03-09 (identification), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes

- ☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- ☒ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- ☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;
- ☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Kurtis R. Bray, Ph.D.	Principal Staff Clinical Scientist
FIRM/ORGANIZATION: Beckman Coulter, Inc.	
SIGNATURE: Kurtis R. Bray	Date (mm/dd/yyyy): 04/10/2012

See following page for details.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Details of Disclosable Financial Arrangements Between Denise L. Geiger, Ph.D. and Beckman Coulter (BCI) During 2009.

During the year 2009, in which the multi-site study titled Reference Interval Study for Access® Immunoassay AccuTnI Assay Protocol#: TnI-03-09 was conducted, and for which Dr. Geiger was a principal investigator for one of the sites, a prior consulting agreement between Dr. Geiger and BCI was in still force. This agreement called for Dr. Geiger to provide consultation and professional advice of a general nature concerning clinical chemistry and laboratory science. For this service she was paid $170/hour for the first five hours of consultation per month and $100/hour for any hours in excess of five per month.

Under this agreement Dr. Geiger provided professional advice on a wide variety clinical laboratory, clinical chemistry, and immunoassay issues unrelated to this study. This agreement had no direct or indirect effect on the conduct of TnI-03-09, since Dr. Geiger's role in that study was to oversee the enrollment of normal, healthy individuals as defined by the inclusion and exclusion criteria provided by the sponsor.

Steps taken to eliminate any potential bias include:
1) Consecutive enrollment
2) Enrollment was governed by a detailed set of inclusion and exclusion criteria previously developed by the sponsor (BCI).
3) Validity of information included on the case report forms was ensured by monitoring against source documents conducted by the sponsor.
4) The sponsor was the sole final judge of any subject's suitability for inclusion in the study.

Thus no bias was introduced into the study by these disclosed arrangements.

Kurtis R. Bray, Ph.D.
Name

Principal Staff Clinical Scientist
Title

Beckman Coulter, Inc
Firm/Organization

Signature

4/10/2012
Date

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Form FDA 3454: Feasibility Efficacy Trial

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Food and Drug Administration

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Expiration Date August 31, 2012

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator		
	Jin Ho Han, MD, MSc	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Kurtis Bray, PhD	Principal Staff Clinical Scientist
FIRM/ORGANIZATION Beckman Coulter, Inc.	
SIGNATURE Kurtis R. Bray	DATE (mm/dd/yyyy) March 15 2012

Paperwork Reduction Act Statement

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Form FDA 3454: Pivotal Efficacy Trial

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Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached List	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Kurtis Bray, PhD	Director of Clinical Research
FIRM/ORGANIZATION: Beckman Coulter, Inc.	
SIGNATURE: Kurtis Bray	DATE (mm/dd/yyyy): 04/29/2011

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FORM FDA 3454 (10/09)

Pivotal Efficacy Trial Enrollment Sites

Site	Principal Investigator	Institution
1	Jon W. Schrock, MD, FACEP, FAHA	Case Western Reserve School of Medicine MetroHealth Medical Center
2	Alan H. B. Wu, PhD, DABCC, FACB	University of California San Francisco San Francisco General Hospital and Trauma Center
4	Deborah B. Diercks, MD, MSc	University of California Davis Health System
6	Alan B. Storrow, MD	Vanderbilt University Medical Center
7	Richard Nowack, MD, MBA	Henry Ford Health System
8	Erik B. Kulstad, MD, MS	Advocate Christ Medical Center
9	Daniel P. Zelinski, MD, PhD	The Ohio State University Medical Center
10	Frank LoVecchio, DO, MPH, FACEP	Maricopa Medical Center
11	Adam J. Singer, MD	Stony Brook University Medical Center State University of New York (SUNY) at Stony Brook
12	Christopher J. Hogan, MD	Virginia Commonwealth University Medical Center
13	Gary F. Headden, MD	Medical University of South Carolina
14	Christian Fromm, MD, FAAEM, FACEP	Maimonides Medical Center
15	Marna R. Greenberg, DO, MPH	Lehigh Valley Hospital
16	Tracie I. Shea, MD	Covenant Medical Center

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Form FDA 3454: Specimen Testing Laboratories

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator		
	William L. Roberts, MD, PhD	Deborah H. Sun, PhD
	Gabrini Delaney	James C. Ritchie, PhD, DABCC, FACB
	Robert H. Christenson, PhD, DABCC, FACB	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Kurtis Bray, PhD	Principal Staff Clinical Scientist
FIRM/ORGANIZATION: Beckman Coulter, Inc.	
SIGNATURE: Kurtis R. Bray	DATE (mm/dd/yyyy): March 15, 2012

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Form FDA 3454: Independent Central Adjudication Panel

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CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Christopher del Filippi, MD	Christian Ruff, MD
	Gautam Ramani, MD	
	Robert Gargiulo, MD	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Kurtis Bray, PhD	Director of Clinical Research
FIRM/ORGANIZATION: Beckman Coulter, Inc.	
SIGNATURE: Kurtis Bray	DATE (mm/dd/yyyy): 04/29/2011

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9.18. Attachment VI: Pivotal Efficacy Trial Protocol And Case Report Forms

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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INVESTIGATIONAL PLAN
CLINICAL STUDY PROTOCOL

STUDY TITLE: **Evaluation of the Beckman Coulter AccuTnI® Assay as an Aid in the Diagnosis of Myocardial Infarction (MI)**

PROTOCOL NUMBER: **TnI-2-10**

APPROVAL DATE: **July 14, 2010**

SPONSOR: **Beckman Coulter, Inc.**

PROTOCOL AUTHOR: **Paula C. Southwick, PhD, CCRA, RAC**
Group Manager, Clinical Research
2470 Faraday Ave.
Carlsbad, CA 92010
760-438-6578
pcsouthwick@beckman.com

For Investigational Use Only: The Performance Characteristics Of This Product Have Not Been Established.

CONFIDENTIALITY STATEMENT

This document contains information that is privileged or confidential and may not be disclosed unless such disclosure is required by Federal or State law or regulations. This information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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TABLE OF CONTENTS

		Page
A.	BACKGROUND	3
B.	STUDY OBJECTIVE	3
C.	INTENDED USE	3
D.	EXPERIMENTAL METHOD	3
	o Study Design and Methods	3
	o Sites	3
	o Number of Subjects and Duration of Study	3
	o Predicate TnI Assay	4
	o Study Subjects	4
	o Inclusion Criteria	4
	o Exclusion Criteria	4
	o Universal Definition of Myocardial Infarction (MI)	4
	o Final Diagnosis: Investigational Site, Principal Investigator	5
	o Final Diagnosis: Central Adjudication Panel	5
	o Phone Follow-up	5
	o Patient Characterization, Comorbidities, Cardiovascular-Related Conditions	5
	o Control of Bias, Blinding	5
	o Blood Sample Collection, Specimen Types, Storage, and Testing	6
E.	STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE RATIONALE	7
F.	INVESTIGATIONAL PRODUCT DESCRIPTION	8
G.	ETHICAL CONSIDERATIONS	8
	o Risk / Benefit Assessment	8
	o Institutional Review Board / Independent Ethics Committee (IRB/IEC) Approval	9
	o Informed Consent	9
	o Subject Confidentiality	9
H.	STUDY MONITORING AND OVERSIGHT	9
	o Case Report Forms (CRFs)	9
	o Source Documents	10
	o Investigator Study Files	10
	o Records Retention	10
	o Sponsor Monitoring / Quality Assurance	10
I.	INVESTIGATOR AND SPONSOR OBLIGATIONS	11
	o Investigator Obligations	11
	o Sponsor Obligations	11

APPENDIX 1: SAMPLE SUBJECT INFORMED CONSENT FORM

APPENDIX 2: CASE REPORT FORMS (CRFs)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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A. BACKGROUND

- The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (TnI) levels in human serum and plasma using the Access Immunoassay Systems to aid in the diagnosis of myocardial infarction (MI).

- Over the past 15 years since clearance of the first troponin assay, diagnosis of myocardial infarction have evolved. Consensus guidelines have emerged that promote the use of more sensitive troponin assays and lower cutoffs, specifically the 99th percentile of the Upper Reference Limit (URL).

B. STUDY OBJECTIVE

- The study objective is to evaluate the clinical utility of the AccuTnI assay as an aid in the diagnosis of myocardial infarction, using the 99th percentile URL cutoff.

- Sensitivity (% MI correctly identified) and Specificity (% Non-MI correctly identified) will be calculated over time from serial draws up to 24 hours from presentation. Positive and negative predictive values will also be reported.

C. INTENDED USE

- The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (TnI) levels in human serum and plasma using the Access Immunoassay Systems to aid in the diagnosis of myocardial infarction.

D. EXPERIMENTAL METHOD

Study Design and Methods

- Multicenter prospective cohort study enrolling Emergency Department (ED) patients with suspected Acute Coronary Syndromes (ACS)

Sites

- Multicenter (10 to 20 sites or more)
- Hospital-associated Emergency Departments (although a limited number of cardiac specialty or tertiary care centers may be included)
- Principally US sites (a limited number of OUS sites may be included)
- Diagnosis and treatment of patients at each site will use an FDA-cleared predicate TnI assay other than AccuTnI

Number of Subjects and Duration of Study

- Approximately 1,200 subjects, assuming an AMI incidence of ~6% and clinical sensitivity of 95%. (See "Statistical Analysis Plan and Sample Size Rationale" for details.)
- Approximately 60 to 200 subjects per site (maximum # of subjects allowed per site = 500)
- Approximately 4 to 6 months for subject enrollment

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Predicate TnI Assay

- Siemens ADVIA Centaur Immunoassay System, TnI-Ultra Assay

Study Subjects

- This study will evaluate patients presenting to the ED with chest pain or equivalent ischemic symptoms suggestive of ACS with the following criteria.
  - **Inclusion Criteria**
    - Subject clinical history must be available for review by sponsor and FDA or other regulatory agencies
    - Written Informed Consent obtained
    - ≥21 years of age
    - Presentation to the ED with chest discomfort or equivalent ischemic symptoms occurring at rest, lasting ≥5 min, and consistent with myocardial ischemia (chest pain, shortness of breath, left arm pain, lightheadedness, dizziness, weakness, and syncope)
    - 12-lead ECG taken at time of presentation to the ED
    - A minimum of 3 blood draws within 24 hours of presentation is desirable (collected at presentation and at every standard-of-care follow-up draw). However, 2 blood draws are acceptable when immediate intervention is required per standard-of-care, and a 3rd draw could not be obtained without delaying treatment.

      (Restricting the study to only those subjects with ≥3 samples would lead to selection bias by eliminating the majority of MI patients who receive timely reperfusion therapy per the American Heart Association's "Get With The Guidelines" recommendations.)
    - A final diagnosis (MI vs non-MI)
  - **Exclusion Criteria**
    - Prior participation in this study (i.e. subjects may not be enrolled more than once in this study)
    - Current participation in an investigational device or drug study (with the exception of other IVD blood test studies, which are acceptable)

Universal Definition of Myocardial Infarction (MI)

- Final diagnosis will be based on the Universal Definition of Myocardial Infarction (MI), defined as follows (Thygesen et al. Circulation 2007;116:2634-2653):
  - Detection of rise and/or fall of cardiac biomarkers (preferably troponin)
  - With at least one value above the 99th percentile of the URL
  - With evidence of myocardial ischemia, with at least one of the following:
    - Symptoms of ischemia
    - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB))
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Note: The troponin assay used for diagnosis of patients at each site will be an FDA-cleared predicate TnI assay which is the standard of care at each institution.

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Final Diagnosis: Investigational Site, Principal Investigator

- Final diagnoses will be adjudicated by the site's principal investigator or clinician with expertise in the diagnosis of MI, using all medical records and CRFs for each patient. Investigators and clinicians will be blinded to the AccuTnI assay results but will have access to the standard-of-care troponin used at the institution.

Final Diagnosis: Central Adjudication Panel

- In addition to the site's determination of a final diagnosis, a central Adjudication Panel will also be used in this study. Case Report Forms (CRFs) for all patients from all sites will be sent to this Panel in order to ensure standardization of diagnoses.
- A final diagnosis of myocardial infarction for each patient will be determined by this central Adjudication Panel of three members with clinical expertise in the diagnosis of MI. These reviewers will be blinded to the AccuTnI assay results and attending physicians' diagnosis, but will have access to the standard-of-care troponin used at each institution recorded on the CRFs. Non-agreements in diagnosis following review of the CRFs by two expert panelists will be adjudicated by a third panelist.

Phone Follow-up

- In cases where the diagnosis is indeterminate and additional follow-up information may be required, patients (or alternate contacts) may be contacted by phone to determine any post-hospitalization cardiac events, and to provide additional relevant medical information for adjudication.

Patient Characterization, Comorbidities, Cardiovascular-Related Conditions

- Case Report Forms (CRFs) will collect final diagnosis and co-existing disease for all study subjects, including underlying conditions that may cause cardiac muscle damage and elevate TnI. Anticipated conditions include heart failure, myocarditis, cardiomyopathy, pulmonary embolism, prior cardiac surgery, or other conditions such as trauma, infection (e.g. sepsis), cardiotoxic drugs, or renal failure that may cause myocardial injury.

Control of Bias, Blinding

- Clinicians will not be provided with AccuTnI results prior to assessment of patient clinical status. Laboratorians will not be provided with clinical status prior to determination of AccuTnI results.
- Patients will be enrolled in a controlled consecutive manner.
- Sites and patient populations representative of the intended use population will be selected (patients presenting to the ED with chest pain or equivalent ischemic symptoms suggestive of ACS). Non-representative study populations produce inaccurate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) results.*
    - The incidence of acute coronary syndromes (ACS: MI and unstable angina) in the US in patients presenting with chest pain in hospital emergency departments is approximately 8% to 25%.* This is the incidence anticipated in this study. Studies with incidence higher than this will overestimate apparent diagnostic accuracy.*

*Jaffe AS and Apple FS. High sensitivity cardiac troponin: Hype, help and reality. Clin Chem 2010;56:342-344.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Blood Sample Collection, Specimen Types, Storage, and Testing

- After informed consent has been obtained, each patient will be assigned a unique patient identifier number ("Patient Study ID Number").
- Blood will be collected at presentation and at every standard-of-care follow-up draw based on current practice.
  - A minimum of 3 blood draws within 24 hours of presentation is desirable. However, 2 blood draws are acceptable when immediate intervention is required per standard-of-care, and a 3rd draw could not be obtained without delaying treatment.
  - Data will be analyzed for the following blood draw time frames (time from admission):
    - Admission (time 0)
    - 2 hours (range 1-3)
    - 4 hours (range 3-6)
    - 8 hours (range 6-10)
    - >10 hours (range 10-24)
  - Time of symptom onset, time of admission, and times of all blood draws will be recorded to allow statistical analysis of assay performance for each time point tested.
- Matched sample types will be collected at each blood draw time:
  - Serum: 8.5 mL of blood in a serum separator tube (SST, red-gray top)
  - Lithium heparin plasma: 8 to 10 mL of blood in a lithium heparin plasma tube (green top) or lithium heparin plasma separator tube (PST, green-gray top)
- Observe the following recommendations for handling, processing, and storing blood samples (ensure sample tube manufacturer recommendations are followed).
  - Collect the serum tube first, followed by the plasma tube.
  - Allow serum samples to clot completely before centrifugation.
  - Centrifuge the samples within 2 hours of blood draw.
  - Serum or plasma should be physically separated from contact with cells or gel immediately after centrifugation.
  - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
  - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
  - Dispense 2 to 6 aliquots of each sample type (serum, plasma) into cryovials (0.5 mL per cryovial). (Note: A minimum of 1 mL serum and 1 mL plasma per draw is required.) Each cryovial will be barcode-labeled with the unique patient identifier number and sample type.
  - Store cryovials in a -20° C or colder freezer immediately (or no longer than 4 hours after preparing aliquots).
- **A log will be maintained** with the following information corresponding to barcode labels: unique patient identifier number, blood draw dates and times, and sample type (serum or plasma).
- AccuTnI and Predicate TnI testing will be performed at each institution, or frozen samples will be batch shipped for testing at a central laboratory.
- Following instructions from the Beckman Coulter Inc. (BCI) Clinical Trial Monitor, ship the frozen samples to BCI.
- Site will be provided with barcode-labeled specimen tubes and cryovials, shipping supplies (not including dry ice) and mailing labels.
- The stored frozen samples may also be tested in the future to evaluate new instrument platforms, assay modifications, or other potential cardiac biomarkers.

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E. STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE RATIONALE

- Clinical Utility
  - Study Endpoint: Myocardial Infarction (MI) vs Non-Myocardial Infarction (Non-MI)
  - Sensitivity (% MI correctly identified) and Specificity (% Non-MI correctly identified) for the 99th percentile URL will be determined for multiple time frames after symptom onset and after admission to the hospital.
    - Data will be analyzed for the following blood draw time frames (time from admission):
      - Admission (time 0)
      - 2 hours (range 1-3)
      - 4 hours (range 3-6)
      - 8 hours (range 6-10)
      - >10 hours (range 10-24)
    - Time frames may be combined if sample size is inadequate in any individual window, in order to improve the accuracy of sensitivity and specificity estimates over time.
    - Data will also be analyzed in a similar manner for multiple time frames after symptom onset.
  - Note that AccuTnI diagnostic accuracy may be underestimated if patient diagnoses are based on later hospital draw times where samples are not available for AccuTnI testing. The Case Report Forms (CRFs) will collect all standard-of-care troponin values obtained at the hospital for each patient, in order to determine the extent to which this has occurred.
  - Sensitivity and Specificity results will be compared for the AccuTnI Assay and Predicate TnI Assay, using the 99th percentile URL for each assay. Positive predictive value (PPV) and negative predictive value (NPV) will also be reported.
  - Sensitivity and Specificity results will also be calculated for relative (%) and absolute (ng/mL) changes in marker concentrations over time to determine optimal delta values, and to assess whether measuring change adds incrementally to diagnostic performance.
  - The sample size required for a 95% two tailed confidence interval about a proportion is shown in the table below for possible Sensitivity and Specificity results.
  - In the following equation, n is the sample size, z is the standard normal variate corresponding to the degree of confidence (1.96 for 95% CI), P is the estimate of sensitivity or specificity, and d is the half-width of the confidence interval (e.g. 5%):

$$n = z^2 P (1-P) / d^2$$

Sample Size (Proposed Calculation from Draft CLSI EP24)

Possible Sensitivity or Specificity Results	Minimum Sample Size Required (MI or Non-MI Patients)
95% ± 5%	73
90% ± 5%	139
85% ± 6%	136
80% ± 7%	126
70% ± 8%	126
60% ± 9%	114
50% ± 10%	96

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- Assuming clinical sensitivity of 95%, a minimum of 73 MI patients is required. Assuming clinical sensitivity of 90%, a minimum of 139 MI patients is required.
- The incidence of acute coronary syndromes (ACS: MI and unstable angina) in the US in patients presenting with chest pain in hospital emergency departments is approximately 8% to 25%.
  - However, assuming an incidence of MI alone of ~6%:
    - Approximately 1,200 patients presenting with chest pain would be required to yield 73 MI patients and 1,127 Non-MI patients.
    - Approximately 2,300 patients presenting with chest pain would be required to yield 139 MI patients and 2,161 Non-MI patients.
- Incidence assumptions will be monitored throughout the trial. Subject accrual will stop when an adequate number of MI patients are enrolled to obtain an accurate estimate of Sensitivity.
- Controlled consecutive enrollment of all patients meeting study entry criteria will produce an excess of Non-MI patients. An accurate estimate of Specificity will therefore be obtained under any scenario in which sufficient MI subjects are enrolled.

- Other Analyses
  - Additional analyses will compare the AccuTnI assay to an FDA-cleared predicate cardiac troponin I (TnI) assay, using native patient samples from the intended use population with expected troponin values in the clinically relevant range.
    - Method Comparison (Deming or Passing Bablok regression).
    - Concordance (2x2 table, percent agreement) using 99th percentile URLs.
    - Note that the majority of samples will be in the clinically important low end of the assay range (primarily up to 1 ng/mL) and will not span the reportable range of the assay (up to 100 ng/mL).
    - A minimum of 100 patient samples (one sample per patient) is required for these analyses, but a much larger sample size is anticipated (see Clinical Utility section above).

F. INVESTIGATIONAL PRODUCT DESCRIPTION

- Beckman Coulter Access 2 Immunoassay System, AccuTnI Assay
- Beckman Coulter UniCel DxI Access Immunoassay System, AccuTnI Assay
- Predicate: Siemens ADVIA Centaur Immunoassay System, TnI-Ultra Assay

G. ETHICAL CONSIDERATIONS

Risk / Benefit Assessment

- The study protocol does not require patients to undergo any procedure that would not already have been performed as part of their standard medical care. Extra tubes of blood will be collected at presentation and at every standard-of-care follow-up draw.
- The risks to the subject include the mild discomfort of the needle stick plus the minimal possibility of hematoma.
- Subjects will not be told the results from the AccuTnI assay.
- Physicians will not base any medical decisions or diagnoses on this test, and will not change any medications based on this test. Medical care will not be affected by this test.
- The information obtained in this study will not benefit the study subjects directly, but may aid future patients by helping to improve the diagnosis and treatment of myocardial infarction.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Institutional Review Board / Independent Ethics Committee (IRB/IEC) Approval

- The protocol and informed consent form require review and approval by each site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
- Copies of all correspondence between the investigator and the IRB/IEC should be kept in the investigator's site study file (Site Study Binder(s)).
- A copy of the IRB letter approving the study protocol and informed consent form must be sent to the Sponsor within two weeks of receipt by the investigator.

Informed Consent

- Written signed informed consent will be obtained from each subject. It is the responsibility of the investigator to obtain informed consent, and to provide the subject with a copy of the signed and dated consent form.
- The consent form, as approved by the site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC), must comply with FDA regulations (Protection of Human Subjects, 21CFR50), the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and the Declaration of Helsinki.
- A sample Subject Informed Consent Form is attached as an Appendix to this protocol to assist the investigator. If any of the language in this form is changed to meet the particular needs of the institution, the Sponsor must review the revised form prior to initiation of the study.

Subject Confidentiality

- Information collected for this study is confidential. However, officials of the Food and Drug Administration (FDA) or other regulatory agencies may inspect patient medical records during the ordinary course of carrying out their functions. A representative of the Sponsor may also inspect these research records to make certain the study data are accurate. The Investigator, Institution, regulatory agencies, and Sponsor will protect the confidentiality of the records. In the event of any publication regarding this study, patient identities will not be disclosed.
- Each patient will be assigned a unique patient identifier number (Patient Study ID Number), and all Case Report Forms and blood samples will be labeled with this ID number. A Subject Enrollment Log will be maintained at the study site, matching subject name to ID number. Any documents with subject names must be kept at the study site and must not be sent to the Sponsor. However, as noted above, records must be available for on-site inspection by the Sponsor or regulatory agencies to ensure that data submitted to the Sponsor are accurate.

H. STUDY MONITORING AND OVERSIGHT

Case Report Forms (CRFs)

- Case Report Forms (CRFs) will be completed for each subject. CRFs should be completed within 1 to 2 weeks after the subject's study blood draws. CRF completion soon after enrollment allows the Sponsor to detect and clarify any misunderstandings regarding the protocol or CRFs early in the process, preventing duplication of work and saving the site personnel time and effort.
- The Sponsor will send to the site periodic query reports with listings of subjects and CRF data fields requiring clarification or completion.
- If electronic or Web-based CRFs are used:
  - A separate instruction booklet describing data entry procedures, submission of data, periodic query reports, and data correction will be provided to the site, to be inserted into the Site Study Binder(s).
- If paper CRFs are used:
  - Transcribe data in a timely manner from the source documentation (original

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medical records)
- Record all subject data and information in black ballpoint pen on paper CRF
- Complete all fields according to protocol specifications and site initiation training
- Correct errors by striking through the error with a single straight line, making the correction and then dating and initialing the correction. Ensure the original entry is not obliterated by the correction and if necessary, note an explanation or clarification in the CRF margin.

Source Documents

- The investigator will indicate in each subject's original medical records that the subject has been enrolled in this clinical trial. The following study information should be recorded:
  - Sponsor **(Beckman Coulter)**
  - Protocol Number **(TnI-2-10)**
  - Patient Study ID Number
  - Study Enrollment Date (blood draw date)
- Source documents (original medical records, lab reports and data, progress notes, signed informed consent forms, Case Report Forms, etc.) must be available for monitoring and inspection by the Sponsor and appropriate Regulatory agencies (e.g. US FDA).

Investigator Study Files

- Maintain all study records, which include but are not limited to:
  - Protocol
  - IRB approval of the protocol and informed consent form
  - All correspondence with the IRB/IEC, Sponsor, and Regulatory authorities
  - List of subject names and Patient Study ID Numbers
  - Signed informed consent form for all subjects
  - Original medical records for all subjects (source documents)
  - Case Report Forms for all subjects
  - Laboratory data for all subjects
  - Written explanation of any deviations to the protocol
  - Final report to the IRB
- All of the above records should be consolidated in the Study Binder(s) (with the exception of the original medical records, which may be kept elsewhere) and available for inspection by the Sponsor or Regulatory agencies.

Records Retention

- Retain all study records. The investigator must contact the Sponsor and gain written approval prior to destroying any study records.
- If the investigator moves his/her practice, all study records, with the exception or the original medical records, are to be kept with the investigator. The original medical records are to be kept at the study site.

Sponsor Monitoring / Quality Assurance

- The following steps will be taken by the Sponsor or Investigator to assure protocol adherence and accurate, consistent, complete, and reliable data:
  - A start-up training session will be conducted at each site to familiarize the investigators and study coordinators with all sections of the protocol and with the completion of the Case Report Forms.
  - A clinical representative of the Sponsor will make periodic visits to the study sites. The representative will also be available for consultation throughout the study, and on a regular basis will be in contact with the investigator and study coordinator by mail, e-mail, telephone, and fax.
  - The Sponsor will maintain a computerized system to track subject and investigator

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progress. Status reports will be generated for the Sponsor and the investigator to assist in monitoring the study. Standard computer edits will be used to detect missing data or data errors. A clinical representative of the Sponsor will also review and evaluate the Case Report Form data.

- A close-out monitoring visit will be conducted at each site to bring the study to a close and to retrieve and account for all remaining clinical data and subject specimens. The close-out visit will also ensure all study documents and records are on file, and to review regulatory requirements regarding records retention and IRB/IEC reporting requirements

- Records of laboratory tests, clinical notes, and patient medical records will be kept in the patient files at the clinical sites as original source documents for the study. The investigator will retain copies of the completed Case Report Forms. A clinical representative of the sponsor will audit the original source documents and Case Report Forms at the study site.

I. INVESTIGATOR AND SPONSOR OBLIGATIONS

Investigator Obligations

- Obtain Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol and informed consent document, and provide a copy of the approval document to the Sponsor.
- Obtain written informed consent from each subject.
- Ensure that the study is conducted according to the signed research agreement and protocol.
- Comply with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements, and not enroll any subjects until all necessary approvals have been obtained.
- Submit data to the Sponsor on a regular basis as subjects are enrolled, Case Report Forms are completed, and laboratory results are obtained.
- Handle blood specimens correctly as described in this protocol, and send these specimens to the Sponsor on a timely basis.
- Submit a final report to the IRB/IEC as dictated by the Institution.
- Maintain study records in the Site Study Binder(s) (with the exception of the original medical records, which may be kept elsewhere).
- Retain all study records. The investigator must contact the Sponsor and gain written approval prior to destroying any records.
- Permit monitoring of subjects' records and source documents (original medical records, lab reports, progress notes, signed informed consent forms, Case Report Forms, etc.) by the Sponsor and Regulatory (e.g. FDA) personnel. All study results will be held in confidence.

Sponsor Obligations

- Train and monitor study sites, and provide guidance regarding protocol requirements, Good Clinical Practices and applicable regulatory requirements.
- Communicate regularly with site personnel.
- Ensure that the study is conducted according to the signed research agreement and protocol.
- Ensure that the investigator has obtained IRB approval, and that written informed consent is obtained from each subject.
- Ensure that the data submitted to the Sponsor are accurate and consistent with original source documents.
- Provide site with materials and supplies for shipping of frozen specimens to Sponsor.

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APPENDIX 1
SAMPLE SUBJECT INFORMED CONSENT FORM

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INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Name of Participant:_____

Medical Institution:_____

Principal Investigator:_____

Principal Investigator's Phone Number:_____

Name of Chairperson, Institutional Review Board/Ethics Committee:_____

Chairperson's Phone Number:_____

Title of Study: Evaluation of the Beckman Coulter AccuTnI® Assay as an Aid in the Diagnosis of Myocardial Infarction (MI) (Protocol #TnI-2-10)

Study Sponsored By: Beckman Coulter, Inc., Carlsbad, California, USA

Purpose of the Study:

The purpose of the study is to evaluate a blood test (AccuTnI) that measures troponin, a protein released into the blood by damaged heart muscle.

You may or may not have damaged heart muscle, and your doctor will provide the standard of care to determine your diagnosis. Your medical care and treatment will not be changed by participating in this study.

This study will simply collect extra blood samples to be stored and tested later with the AccuTnI assay.

Over the past 15 years since the first troponin test became available, diagnosis and treatment of heart attacks (myocardial infarction) have changed and progressed. New guidelines encourage the use of more sensitive troponin tests and the use of lower values in order to detect heart attacks earlier. This study will examine how well this new approach will work with the AccuTnI assay.

Your blood samples will also be stored for future testing to evaluate new laboratory instruments, assay modifications, or new blood tests that may improve diagnosis and treatment of heart attacks for patients in the future.

Number and Description of Participants in this Voluntary Research Study:

By signing this form, you agree to participate in a research study at the institution listed above. The study will involve up to several thousand Emergency Department patients who have chest pain or other symptoms that might suggest possible heart problems. Most of the patients will actually turn out not to have any heart problems, but about 5% to 10% will be diagnosed with a heart attack.

About 5 to 10 medical institutions or more will participate in this study.

Your participation in this study is entirely voluntary. You may refuse to participate or withdraw your consent at any time without penalty or loss of benefits. If you decide to stop taking part in this study, you will tell the investigator or study coordinator.

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Your doctor, the investigator and/or the sponsor may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions. If you have other medical problems, the doctor and/or nurse will decide if you may continue in the research study.

Study Procedures, Length of Participation:

As part of your standard medical care, blood samples will be obtained from a vein in your arm. You agree to provide two extra tubes of blood (less than 4 teaspoons) at admission and at every routine follow-up blood draw based on current practice after arriving at the Emergency Department. Your study participation will end when a diagnosis is made or up to 24 hours after admission.

The study coordinator will also complete a medical history form using information from your medical chart and information you provide. This information will include your date of birth, sex, race, medical history, medications, symptoms, diagnosis, procedures performed, and laboratory results.

Possible Study Risks:

Extra tubes of blood will be collected whenever you have your blood drawn as part of your standard evaluation. This study does not require you to undergo any procedures that would not already have been performed as part of your routine medical care.

Obtaining blood may sometimes cause mild pain, bleeding, bruising, or swelling at the site of the needle stick.

You will not be told the results from this test since the purpose of the study is to assess how well it performs. Your doctor will not base any medical decisions or diagnosis on this test, and will not change your medications based on this test. Your medical care will not be affected by this test.

Phone Follow-up:

In cases where the final diagnosis is not clear or additional follow-up information is required, you (or an alternate contact person who you specify) may be contacted by phone to determine any post-hospitalization heart problems, and to obtain additional medical information.

Possible Benefits for Taking Part in the Study:

The information obtained in this study will not benefit you directly, but may aid future patients by helping to improve the diagnosis and treatment of heart attacks.

Costs and Payments for Taking Part in This Study:

There will be no financial benefit to you as a result of your participation in this study, nor will it cost you anything to participate in this study. You or your insurance company will pay for your standard medical care.

Confidentiality of Study Records and Medical Records:

Information collected for this study is confidential. However, your medical records may be inspected by officials of the Food and Drug Administration (FDA) or other regulatory agencies during the ordinary course of carrying out their functions. A representative of the Sponsor may also inspect these research records to make certain the study data are accurate. The investigator, institution,

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regulatory agencies, and sponsor will protect the confidentiality of your records. In the event of any publication regarding this study, your identity will not be disclosed.

Names of Contacts for Questions About the Study:

The investigator is willing to answer any questions you may have concerning this study. You may also ask questions or state concerns to the Chairperson of the Institutional Review Board/Ethics Committee. Their contact information is at the top of this Informed Consent Form.

You will be given a copy of this informed consent.

Participant's Signature _____ Date _____

Physician's Signature _____ Date _____

Copy 1: Subject's Copy
Copy 2: Physician's Copy

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

BECKMAN COULTER, INC.
Evaluation of the AccuTnI Assay As An Aid In The Diagnosis of Myocardial Infarction (MI)
Case Report Forms (CRFs) for Protocol Number TnI-2-10 (July 14, 2010)

PATIENT IDENTIFICATION

Patient Study ID Number: B ___ ___ ___ ___ ___
Protocol Code — Site # — Subject # (number patients in consecutive order: 001, 002, 003,...)

INCLUSION CRITERIA (All must be marked "YES" to be included in the study)

Yes	No	
☐	☐	Subject clinical history must be available for review by sponsor and FDA or other regulatory agencies
☐	☐	Signed written Informed Consent obtained
☐	☐	≥ 21 years of age
☐	☐	Presentation to the ED with chest discomfort or equivalent ischemic symptoms occurring at rest, lasting ≥ 5 min, and consistent with myocardial ischemia (chest pain, shortness of breath, left arm pain, lightheadedness, dizziness, weakness, and syncope)
☐	☐	12-lead ECG taken at time of presentation to the ED
☐	☐	A minimum of 3 blood draws within 24 hours of presentation is desirable (collected at presentation and at every standard-of-care follow-up draw). However, 2 blood draws are acceptable when immediate intervention is required per standard-of-care, and a 3rd draw could not be obtained without delaying treatment.
☐	☐	A final diagnosis (MI vs non-MI)

EXCLUSION CRITERIA (All must be marked "NO" to be included in the study)

Yes	No	
☐	☐	Prior participation in this study (i.e. subjects may not be enrolled more than once in this study)
☐	☐	Current participation in an investigational device or drug study (with the exception of other IVD blood test studies, which are acceptable)

PATIENT DEMOGRAPHIC INFORMATION

Date of Birth: (dd MON yyyy): __ __ ___ ___ ___ ___ ___ ___
e.g. 1 8 D E C 1 9 4 8

Sex:
- ☐ Male
- ☐ Female

Height:
__ __ inches

If Female, Pregnancy Status:
- ☐ Pregnant
- ☐ Not Pregnant
- ☐ Unknown

Weight:
__ __ __ lbs

Race (check all that apply):
- ☐ White
- ☐ Black
- ☐ Asian
- ☐ American Indian or Alaska Native
- ☐ Native Hawaiian or other Pacific Islander
- ☐ Other, Specify: _____
- ☐ Unknown

Ethnicity (check one):
- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Protocol # TnI-2-10
Patient Study ID Number: B (Protocol Code) ___ ___ (Site #) ___ ___ ___ (Subject # (number patients in consecutive order: 001, 002, 003,...)

CARDIAC-RELATED PATIENT MEDICAL HISTORY

Date and Time of Onset of most recent symptoms of Ischemia:
(dd MON yyyy and 24-hour clock) e.g. 1 8 D E C 1 9 4 8 1 7 : 3 0

Note: If exact date and time are not known, please make estimate. Do not leave fields blank.

Symptoms of Ischemia include: Chest Pain/Pressure, Jaw/Neck Pain, Shoulder/Arm Pain, Back Pain, Abdominal Pain, Shortness of Breath, Lightheadedness, Dizziness, Fainting, Weakness, Fatigue, Heart Beat Irregularity, Nausea, Vomiting

Date and Time of Emergency Department (ED) Registration:
(dd MON yyyy and 24-hour clock) e.g. 1 8 D E C 1 9 4 8 1 7 : 3 0

Risk Factors and Comorbidities Present at Time of Hospitalization:

Yes	No	Unknown	
☐	☐	☐	Age ≥ 65 years
☐	☐	☐	Family history of premature Coronary Artery Disease (CAD) (biological parents or siblings, prior to age 55)
☐	☐	☐	Hypertension (HTN)
☐	☐	☐	Dyslipidemia or Hypercholesterolemia
☐	☐	☐	Diabetes Mellitus (DM)
☐	☐	☐	Current Smoker (How many years have you smoked? _____ years)
☐	☐	☐	Past Smoker (How many years did you smoke? _____ years)
☐	☐	☐	Aspirin in past 7 days
☐	☐	☐	Recent severe angina (≥ 2 anginal events in last 24 hours)
☐	☐	☐	ST segment deviation ≥ 0.5 mm on ECG at presentation
☐	☐	☐	Known Coronary Artery Disease (CAD), documented stenosis > 50%
☐	☐	☐	Prior Acute Myocardial Infarction (AMI)
☐	☐	☐	Prior Coronary Artery Stent or Angioplasty
☐	☐	☐	Prior Coronary Artery Bypass Graft (CABG)
☐	☐	☐	Prior Stroke or Cerebral Vascular Accident
☐	☐	☐	Heart Failure (HF)
☐	☐	☐	Peripheral Vascular Disease (PVD) or Peripheral Artery Disease (PAD)
☐	☐	☐	Chronic Kidney Disease or Chronic Renal Insufficiency
☐	☐	☐	Other (specify):_____

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Protocol # TnI-2-10
Patient Study ID Number: B (Protocol Code) ___ ___ (Site #) ___ ___ ___ (Subject # (number patients in consecutive order: 001, 002, 003,...)

CARDIAC-RELATED PATIENT MEDICATION HISTORY

Current Cardiac-Related Medications Taken Before ED Visit :

Yes	No	Unknown	
☐	☐	☐	ACE inhibitor (e.g., captopril, vasotec)
☐	☐	☐	Angiotensin II receptor blocker (ARB) (e.g., valsartan)
☐	☐	☐	Beta-blocker (e.g., atenolol, metoprolol)
☐	☐	☐	Calcium channel blocker (e.g., diltiazem, verapamil)
☐	☐	☐	Coumadin
☐	☐	☐	Diuretic (e.g., furosemide, metolazone)
☐	☐	☐	Low-molecular weight heparin (e.g., enoxaparin)
☐	☐	☐	Nitrate (e.g., isosorbide, nitroglycerin)
☐	☐	☐	Platelet inhibitor (e.g., Clopidogrel [Plavix], dipyridamole)
☐	☐	☐	Statin (e.g., lovastatin, atorvastatin)

MEDICATIONS PROVIDED AFTER ED PRESENTATION

Cardiac-Related Medications In the ED or Hospital:

Record Date and Time of first administration of drug:

Yes	No			
☐	☐	Fibrinolytic / thrombolytic (e.g. alteplase)	Date__ __ __ __ __ __ __ __	Time__ __:__ __
☐	☐	Unfractionated Heparin	Date__ __ __ __ __ __ __ __	Time__ __:__ __
☐	☐	Low-molecular weight heparin (e.g. enoxaparin)	Date__ __ __ __ __ __ __ __	Time__ __:__ __

(dd MON yyyy and 24-hour clock): e.g. 1 8 D E C 1 9 4 8 1 7 3 0

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Protocol # TnI-2-10
Patient Study ID Number: B (Protocol Code) ___ (Site #) ___ (Subject # (number patients in consecutive order: 001, 002, 003,...))

PATIENT CARDIAC TESTING PERFORMED DURING CURRENT HOSPITALIZATION

Describe testing performed during current hospitalization:

ECG Results:

Yes No
☐ ☐ ECG changes indicative of new ischemia (new ST-T changes or new LBBB)

Yes No
☐ ☐ Development of pathological Q waves

ECG Comments (optional) (200 character limit): _____

Imaging Evidence of MI:

Yes No
☐ ☐ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

If yes, specify imaging technique(s) (e.g. echocardiography, radionuclide techniques, MRI, angiogram, etc.):

_____

PATIENT CARDIAC PROCEDURES PERFORMED DURING CURRENT HOSPITALIZATION

Describe procedures performed during current hospitalization:

Cardiac Catheterization:

Yes No
☐ ☐ Was Cardiac Catheterization performed?

If Yes, Date and Time of Catheterization: Date__ __ __ __ __ __ __ __ Time__ __:__ __
(dd MON yyyy and 24-hour clock) e.g. 1 8 D E C 1 9 4 8 1 7 3 0

If Yes, Number of Coronary Arteries or Grafts with greater than 50% occlusion: ____ ☐ Unknown

Catheterization Comments (optional) (200 character limit): _____

Revascularization Procedures:

Yes No
☐ ☐ Angioplasty
☐ ☐ Stent placement
If Yes, specify number of stents:_____ ☐ Number of stents unknown
☐ ☐ Coronary Artery Bypass Graft (CABG)
If Yes, specify number of grafts:_____ ☐ Number of grafts unknown
☐ ☐ Other percutaneous coronary intervention (PCI), describe:_____

If Yes to Any of the Above Procedures, Date and Time of Revascularization:
Date__ __ __ __ __ __ __ __ Time__ __:__ __
(dd MON yyyy and 24-hour clock) e.g. 1 8 D E C 1 9 4 8 1 7 3 0

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Protocol # TnI-2-10
Patient Study ID Number: B ___ ___ ___ ___ ___
Protocol Code | Site # | Subject # (number patients in consecutive order: 001, 002, 003,...)

PATIENT LABORATORY TESTING PERFORMED DURING CURRENT HOSPITALIZATION

Describe laboratory testing performed during current hospitalization.

Specify the troponin cutoff used to aid in the diagnosis of this patient: 0.___ ___ ng/mL

Specify the standard-of-care troponin assay used at the hospital to aid in the diagnosis of this patient (the assay used to generate the troponin values entered in the table below). Check one:

- ☐ Siemens ADVIA Centaur TnI-Ultra
- ☐ Siemens Dimension TNI
- ☐ Siemens Stratus CS
- ☐ Siemens VISTA
- ☐ Abbott ARCHITECT STAT TnI
- ☐ Abbott AxSYM Troponin-I ADV
- ☐ Inverness Biosite Triage Cardiac Panel
- ☐ Ortho Clinical Diagnostics VITROS Troponin I ES
- ☐ Roche Elecsys Troponin I
- ☐ Other, Specify: _____

Standard of Care Troponin (Troponin reported at hospital)	DATE OF BLOOD DRAW (dd MON yyyy) (e.g. 18 DEC 1948)	TIME OF BLOOD DRAW (24-hour clock) (e.g. 17:30)	RESULT (ng/mL)	Check if Result is Not Detectable
TnI – 1st draw			___.___	☐
TnI – 2nd draw			___.___	☐
TnI – 3rd draw			___.___	☐
TnI – 4th draw			___.___	☐
TnI – 5th draw			___.___	☐
TnI – 6th draw			___.___	☐
TnI – 7th draw			___.___	☐
TnI – 8th draw			___.___	☐

Standard of Care CKMB	DATE OF BLOOD DRAW (dd MON yyyy) (e.g. 18 DEC 1948)	TIME OF BLOOD DRAW (24-hour clock) (e.g. 17:30)	RESULT (ng/mL)	Check if Result is Not Detectable
CKMB – 1st draw			___.___	☐
CKMB – 2nd draw			___.___	☐
CKMB – 3rd draw			___.___	☐
CKMB – 4th draw			___.___	☐
CKMB – 5th draw			___.___	☐
CKMB – 6th draw			___.___	☐
CKMB – 7th draw			___.___	☐
CKMB – 8th draw			___.___	☐

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

FINAL DIAGNOSIS DETERMINED BY PRINCIPAL INVESTIGATOR

Date of Diagnosis: (ddMONyyyy): ___ ___ ___ ___ ___ ___ ___ ___
e.g. 1 8 D E C 1 9 4 8

Check "MI Diagnosis" OR "Non-MI Diagnosis":

- ☐ MI Diagnosis (check one):
  - ☐ NSTEMI (Non-ST elevation myocardial infarction)
  - ☐ STEMI (ST elevation myocardial infarction)
  - ☐ Other (specify): _____
- ☐ Non-MI Diagnosis (check one):
  - ☐ Unstable Angina
  - ☐ Stable Angina
  - ☐ Other Cardiac Diagnosis (specify): _____
  - ☐ Non-Cardiac Diagnosis (specify): _____
  - ☐ Unknown

Other Cardiovascular-Related Complications or Conditions During ED or Hospitalization (check all that apply):

- ☐ Cardiac rupture/ Ventricular septal defect
- ☐ Cardiac tamponade
- ☐ Cardiogenic shock
- ☐ Atrial fibrillation/flutter (new onset)
- ☐ High-degree atrioventricular block (second or third degree)
- ☐ Supraventricular tachycardia (requiring treatment)
- ☐ Ventricular tachycardia (requiring treatment)
- ☐ Ventricular fibrillation (requiring treatment)
- ☐ Cardiotoxic drugs (specify): _____
- ☐ Renal Failure
- ☐ Heart Failure
- ☐ Pulmonary Embolism
- ☐ Hemorrhagic Stroke
- ☐ Ischemic Stroke
- ☐ Transient Ischemic Attack (TIA)
- ☐ Myocarditis
- ☐ Infection (e.g. sepsis) (specify): _____
- ☐ Other (specify): _____

DEATH

Yes	No	
☐	☐	Did patient die during this hospitalization? If Yes, Date of death: (ddMONyyyy): ___ ___ ___ ___ ___ ___ ___ ___ e.g. 1 8 D E C 1 9 4 8
☐	☐	Was cause of death the same as Final Diagnosis? If No, specify cause of death: _____

COMMENTS SECTION

Comments on CRF (optional) (200 character limit):

_____

_____

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Protocol # TnI-2-10
Patient Study ID Number: B ___ ___ ___ ___ ___
Protocol Code | Site # | Subject # (number patients in consecutive order: 001, 002, 003,...)

PHONE FOLLOW-UP

In cases where the diagnosis is indeterminate and additional follow-up information may be required, patients (or alternate contacts) may be contacted by phone to determine any post-hospitalization cardiac events, and to obtain additional relevant medical information.

Was phone follow-up call made? Yes ☐ No ☐

Date of Phone Call: (ddMONyyyy): __ __ ___ ___ ___ ___
e.g. 1 8 D E C 1 9 4 8

Person Contacted:
☐ Patient
☐ Alternate contact

Significant Notes (200 character limit)
(Indicate important information relating to the patient's final diagnosis obtained from this phone call that is not captured elsewhere in these forms. If the information is captured elsewhere, it is not necessary to repeat it here.)

_____

_____

_____

_____

Was second phone follow-up call made? Yes ☐ No ☐

Date of Phone Call: (ddMONyyyy): __ __ ___ ___ ___ ___
e.g. 1 8 D E C 1 9 4 8

Person Contacted:
☐ Patient
☐ Alternate contact

Significant Notes (200 character limit)
(Indicate important information relating to the patient's final diagnosis obtained from this phone call that is not captured elsewhere in these forms. If the information is captured elsewhere, it is not necessary to repeat it here.)

_____

_____

_____

_____

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Protocol # TnI-2-10
Patient Study ID Number: B ___ ___ ___ ___ ___
Protocol Code Site # Subject # (number patients in consecutive order: 001, 002, 003,...)

BECKMAN COULTER, INC.
Evaluation of the AccuTnI Assay As An Aid In The Diagnosis of Myocardial Infarction (MI)
Case Report Forms (CRFs) for Protocol Number TnI-2-10

STUDY BLOOD DRAWS

Enter the date and time for each Study Draw where samples were obtained to provide to Beckman Coulter. Matched serum (S) and lithium heparin plasma (P) sample types will be collected at each blood draw. (Serum samples end in "S" and lithium heparin plasma samples end in "P".)

Study Draws	Date of Blood Draw (dd MON yyyy) *e.g.* 18 DEC 1948	Time of Blood Draw (24-hour clock) e.g. 17:30	Check if Serum Sample Obtained	Record the Serum Barcode Label e.g. Bxx001AS	Check if Li-Hep Plasma Sample Obtained	Record the Li-Hep Plasma Barcode Label e.g. Bxx001AP
A			☐		☐	
B			☐		☐	
C			☐		☐	
D			☐		☐	
E			☐		☐	
F			☐		☐	
G			☐		☐	
H			☐		☐	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

9.19. Attachment VII: Certification of Compliance with Requirements of ClinicalTrials.govData bank

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616. Expiration Date: 2-28-2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
Beckman Coulter, Inc.

2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
April 20, 2012

3. ADDRESS (Number, Street, State, and ZIP Code)
1000 Lake Hazeltine Drive
Chaska, MN 55318

4. TELEPHONE AND FAX NUMBERS (Include Area Code)
(Tel.) 952-448-4848
(Fax) 952-368-7610

PRODUCT INFORMATION

5. FOR DRUGS/BIOLOGICS: Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
(Attach extra pages as necessary)

Access AccuTnI on the Access 2 Immunoassay Systems

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER (If number previously assigned)
N/A

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
N/A

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES (See instructions for additional information and explanation)

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☒ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C. IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES (Attach extra pages as necessary)

NCT Number(s):

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)

12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11
(Name) Kurtis R. Bray
(Title) Principle Staff Clinical Scientist

13. ADDRESS (Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)
2470 Faraday Ave
Carlsbad, CA 92010

14. TELEPHONE AND FAX NUMBERS (Include Area Code)
(Tel.) 760-438-6570
(Fax) 760-438-6502

15. DATE OF CERTIFICATION
Apr 18, 2012

Form FDA 3674 (3/12) (FRONT)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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10.0 Supplemental Information – Field Effectiveness Study

10.1. Introduction

During pre-IDE discussions with the agency on July 8, 2011 concerning the verification and validation of the AccuTnI assay, FDA requested that Beckman Coulter conduct additional assessments to ensure that the thermal algorithm works properly on fielded instruments.

Two "Field Effectiveness" studies were designed to assess whether the precision of the AccuTnI assay when used with the thermal algorithm on the Access 2 instrument meets design specifications:

- *Internal Study*: Internal Algorithm Field Effectiveness Study, conducted at Beckman Coulter
- *External Study*: Clinical Trial Precision, conducted at five external clinical laboratories

Descriptions of each study and results are presented in the following sections.

10.2. Internal Study

Purpose and Scope: This internal study evaluated the precision of the AccuTnI assay used in conjunction with the thermal algorithm on the Access 2 instrument. The assessment was done while using the instrument in simulated run conditions that were designed to simulate customer use. The design incorporated variations that are expected to occur in the field including:

- Simultaneous running of other assays from the Access menu;
- Variability in test request type: panel, reflex, stat, and individual testing;
- Variability of ambient temperatures; and
- Variability of instrument age.

It was necessary to conduct the first study internally due to the requirement to install Investigational Use Only (IUO) Access 2 system software version 3.3 on the instruments. Use of this IUO software would not be appropriate for IVD-labeled instruments that were being used to manage patients in the field.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Furthermore, certain variables can be tested more readily in an internal setting, which allowed us to effectively evaluate the robustness of the AccuTnI assay with the thermal algorithm. **Note:** Additional information on Access 2 system software version 3.3 can be found in Section 6.0.

This study was conducted on three instruments of different ages (manufactured between 2002 and 2010). The IUO AccuTnI assay and a panel of nine additional IVD Access assays, that represent a hospital test menu (Total T4, CK-MB, TSH, Ferritin, Folate, Prolactin, β-hCG, Progesterone, and Total T3), were exercised on three Access 2 instruments over three days.

The ambient temperature of the laboratory was cycled to reflect the worst case thermal profile for Access AccuTnI customers. A six hour thermal program that challenged the full ambient temperature range for AccuTnI was used for each day of the study (see Table 71 below). The thermal program indicates the set temperature that was initiated at the start of each hour of testing; however, the study was run continuously to ensure dynamic temperature changes were also captured.

Table 71: Internal Study Thermal Program

Hour	Set Temperature
1	23°C
2	20.5°C
3	18°C
4	23°C
5	25.5°C
6	28°C

During typical clinical use, the AccuTnI assay may be requested in a number of different ways:

- as part of a cardiac panel
- as a STAT test
- as a reflex test
- as an individual test

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

To simulate field use, tests for all the above assays, including AccuTnI, were randomized for each day of evaluation and distributed throughout the six-hour thermal program. Five cTnI commercial controls were tested with AccuTnI over the course of three days. A minimum of 44 randomized replicates of each sample were tested on each instrument across the three days of testing. (See actual number of replicates in Table 72 below.) A reflex (retest) criterion for AccuTnI was selected (e.g., dose ≥1 ng/mL) such that two of the five samples met the reflex criteria. Samples meeting the reflex criterion yielded a minimum of 88 replicates tested on each instrument over the three days of testing.

Data Analysis: The thermally adjusted variance and unadjusted result variance were calculated for all runs for each control for each instrument. The standard deviation (SD) and coefficient of variation (CV) of each sample for each instrument were also computed for all results.

Acceptance Criteria: The variance of the adjusted results for each sample on each instrument must be less than or equal to the unadjusted results (F-test $p \leq 0.05$). Precision of the adjusted results for the five cTnI samples on each instrument must be ≤8% CV for concentrations >0.105 ng/mL and ≤0.0084 ng/mL standard deviation for concentrations ≤0.105 ng/mL.

Results: Results are provided in Table 72 below.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 72: Internal Algorithm Field Effectiveness Study Results

Instrument ID	Sample ID	(N)	Mean Adjusted Dose (ng/mL)	Unadjusted CV	Unadjusted SD (ng/mL)	Adjusted CV	Adjusted SD (ng/mL)	Ftest	Pass (Y/N)
500537	Biorad LT1	45	0.056		0.0074		0.0023	0.00	Y
	Biorad LT2	45	0.641	12.1%		4.6%		0.00	Y
	Biorad LT3	90	2.040	10.6%		3.7%		0.00	Y
	Biorad Plus 1	45	0.383	8.3%		5.4%		0.00	Y
	Biorad Plus 3	88	8.248	7.2%		5.4%		0.02	Y
504050	Biorad LT1	45	0.055		0.0088		0.0048	0.00	Y
	Biorad LT2	44	0.636	11.4%		4.9%		0.00	Y
	Biorad LT3	87	2.054	11.7%		3.5%		0.00	Y
	Biorad Plus 1	45	0.389	10.5%		6.1%		0.00	Y
	Biorad Plus 3	88	8.348	7.9%		3.8%		0.00	Y
507295	Biorad LT1	45	0.053		0.0072		0.0026	0.00	Y
	Biorad LT2	45	0.594	8.8%		4.6%		0.00	Y
	Biorad LT3	90	1.874	10.5%		3.2%		0.00	Y
	Biorad Plus 1	45	0.366	8.9%		4.9%		0.00	Y
	Biorad Plus 3	88	7.802	7.6%		4.5%		0.00	Y

Conclusion: The acceptance criteria for assay precision were met for results adjusted with the thermal algorithm in the presence of additional expected field variability incorporated into the study.

10.3. External Study - Clinical Trial Precision

Purpose and Scope: The purpose of this study was to evaluate the precision of the AccuTnI assay and using the thermal algorithm at external diagnostic laboratory sites.

All five external sites performed a multi-day precision study on Access 2 instruments to establish QC ranges before beginning to test specimens collected from clinical trial study subjects (Protocol TnI-2-10, see Section 9.0 for additional details on the clinical trial). The study included a minimum of 18 valid runs over ten days and each run included tri-level commercial quality control (QC) samples from two sources (BioRad Laboratories and MORE Diagnostics). The samples were each run in duplicate with three reagent lots on five Access 2 instruments. One Access 2 was utilized at each site; all study Access 2 instruments were dedicated to the study because they were using IUO Access 2 system software version 3.3. The Access 2 instruments represented a wide range of instrument ages (i.e., manufactured from 2001 to 2011).

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Data Analysis: The thermally adjusted and unadjusted result variances were calculated for all runs for each control for reagent lot for each instrument. The standard deviation (SD) and coefficient of variation (CV) of each sample for each instrument were also computed for all results.

Acceptance Criteria: The variance of the adjusted results for each sample greater than the 10% CV LoQ acceptance criteria of 0.06 ng/mL must be less than or equal to the unadjusted results (F-test $p \leq 0.05$). Precision of the adjusted results for all cTnI samples on each instrument must be ≤8% CV for cTnI concentrations >0.105 ng/mL and ≤0.0084 ng/mL standard deviation for cTnI concentrations ≤0.105 ng/mL.

Results: Results are summarized in Table 73 through Table 75 below.

There was a single case in which one of the comparisons of unadjusted and adjusted results did not meet the variance acceptance criteria of $p \leq 0.05$. However, because of the large number of comparisons in this analysis (75) the significance level must be adjusted using the Bonferroni principle where the overall 0.05 alpha must be split between all the comparisons. Thus the significance level for each comparison was recalculated to be $p=0.00067$. At this significance level, none of the unadjusted results had significantly lower variance than the adjusted results.

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Table 73: External Study Clinical Trial Precision Results–Reagent Lot 1

APF 337 - Reagent Lot 1

Site	n	Mean Adjusted Dose (ng/mL)	Adjusted %CV	Adjusted SD	Unadjusted %CV	Unadjusted SD	F-Test	Imprecision Pass (yes/no)	F-Test Pass (yes/no)
UMMC									
Biorad 1	40	0.034		0.0012		0.0026	0.0000	Y	Y
Biorad 2	40	0.626	2.4		4.3		0.001	Y	Y
Biorad 3	40	2.599	2.8		3.8		0.13	Y	Y
ARUP									
Biorad 1	80	0.038		0.0026		0.0027	0.66	Y	Y
Biorad 2	82	0.638	4.3		4.1		0.81	Y	Y
Biorad 3	82	2.647	3.8		3.2		0.18	Y	Y
SBMF									
Biorad 1	40	0.035		0.0049		0.0053	0.59	Y	Y
Biorad 2	40	0.622	3.3		3.2		0.88	Y	Y
Biorad 3	40	2.606	3.6		4.1		0.39	Y	Y
QUES									
Biorad 1	40	0.042		0.0020		0.0022	0.48	Y	Y
Biorad 2	40	0.651	2.5		2.6		0.53	Y	Y
Biorad 3	40	2.586	2.5		2.5		0.89	Y	Y
EMOR									
Biorad 1	36	0.039		0.0031		0.0041	0.09	Y	Y
Biorad 2	40	0.685	4.4		5.1		0.39	Y	Y
Biorad 3	38	2.813	4.3		4.9		0.42	Y	Y
UMMC									
MORE 1	40	0.016		0.0033		0.0019		Y	N/A
MORE 2	40	0.928	3.5		5.9		0.01	Y	Y
MORE 3	40	14.5	1.9		3.1		0.02	Y	Y
ARUP									
MORE 1	80	0.020		0.0041		0.0028		Y	N/A
MORE 2	80	1.028	5.1		4.6		0.39	Y	Y
MORE 3	80	15.03	3.7		3.0		0.04	Y	Y
SBMF									
MORE 1	40	0.011		0.0058		0.0052		Y	N/A
MORE 2	40	0.988	5.2		6.0		0.40	Y	Y
MORE 3	40	15.04	3.5		4.1		0.42	Y	Y
QUES									
MORE 1	40	0.023		0.0013		0.0013		Y	N/A
MORE 2	40	0.97	2.0		2.2		0.44	Y	Y
MORE 3	40	14.19	2.2		2.3		0.84	Y	Y
EMOR									
MORE 1	36	0.016		0.0050		0.0026		Y	N/A
MORE 2	36	1.04	5.2		5.3		0.85	Y	Y
MORE 3	36	16.19	7.4		7.2		0.62	Y	Y

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Table 74: External Study Clinical Trial Precision Results–Reagent Lot 2

APF 344 - Reagent Lot 2

Site	n	Mean Adjusted Dose (ng/mL)	Adjusted %CV	Adjusted SD	Unadjusted %CV	Unadjusted SD	F-Test	Imprecision Pass (yes/no)	F-Test Pass (yes/no)
UMMC									
Biorad 1	40	0.032		0.0017		0.0026	0.010	Y	Y
Biorad 2	40	0.602	3.1		4.2		0.12	Y	Y
Biorad 3	40	2.492	2.8		3.8		0.12	Y	Y
ARUP									
Biorad 1	62	0.032		0.0023		0.0022	0.72	Y	Y
Biorad 2	64	0.623	3.8		3.6		0.65	Y	Y
Biorad 3	64	2.599	3.6		3.6		0.94	Y	Y
SBMF									
Biorad 1	40	0.040		0.0045		0.0048	0.65	Y	Y
Biorad 2	40	0.619	4.3		4.1		0.80	Y	Y
Biorad 3	41	2.56	3.5		4.1		0.37	Y	Y
QUES									
Biorad 1	40	0.039		0.0018		0.0019	0.72	Y	Y
Biorad 2	40	0.626	2.4		2.5		0.59	Y	Y
Biorad 3	40	2.501	2.9		2.8		0.93	Y	Y
EMOR									
Biorad 1	36	0.037		0.0032		0.0041	0.17	Y	Y
Biorad 2	38	0.642	5.0		5.4		0.64	Y	Y
Biorad 3	38	2.68	5.4		6.2		0.49	Y	Y
UMMC									
MORE 1	40	0.013		0.0027		0.0021		Y	N/A
MORE 2	40	0.883	2.8		5.3		0.001	Y	Y
MORE 3	40	13.65	2.2		3.4		0.03	Y	Y
ARUP									
MORE 1	62	0.01		0.0028		0.0023		Y	N/A
MORE 2	62	1.005	5.2		5.5		0.85	Y	Y
MORE 3	62	14.83	3.5		3.4		0.58	Y	Y
SBMF									
MORE 1	40	0.022		0.0064		0.0060		Y	N/A
MORE 2	41	0.978	6.5		6.9		0.79	Y	Y
MORE 3	40	14.87	3.7		4.3		0.44	Y	Y
QUES									
MORE 1	40	0.018		0.0026		0.0014		Y	N/A
MORE 2	40	0.93	2.6		2.7		0.75	Y	Y
MORE 3	40	13.48	1.8		2.0		0.57	Y	Y
EMOR									
MORE 1	36	0.013		0.0050		0.0031		Y	N/A
MORE 2	36	0.968	5.6		5.5		0.69	Y	Y
MORE 3	36	15.19	6.9		6.9		0.74	Y	Y

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Table 75: External Study Clinical Trial Precision Results–Reagent Lot 3

APF 345 - Reagent Lot 3

Site	n	Mean Adjusted Dose (ng/mL)	Adjusted %CV	Adjusted SD	Unadjusted %CV	Unadjusted SD	F-Test	Imprecision Pass (yes/no)	F-Test Pass (yes/no)
UMMC									
Biorad 1	40	0.030		0.0013		0.0020	0.01	Y	Y
Biorad 2	40	0.594	3.2		4.3		0.14	Y	Y
Biorad 3	40	2.455	2.7		3.8		0.09	Y	Y
ARUP									
Biorad 1	62	0.031		0.0027		0.0029	0.57	Y	Y
Biorad 2	63	0.615	4.4		3.9		0.42	Y	Y
Biorad 3	63	2.53	3.3		3.0		0.43	Y	Y
SBMF									
Biorad 1	40	0.034		0.0051		0.0054	0.64	Y	Y
Biorad 2	40	0.601	3.0		3.9		0.11	Y	Y
Biorad 3	40	2.49	3.6		4.2		0.31	Y	Y
QUES									
Biorad 1	40	0.036		0.0016		0.0017	0.71	Y	Y
Biorad 2	39	0.619	2.7		2.6		0.99	Y	Y
Biorad 3	40	2.485	2.4		2.4		0.94	Y	Y
EMOR									
Biorad 1	38	0.035		0.0030		0.0038	0.19	Y	Y
Biorad 2	38	0.645	5.7		6.2		0.67	Y	Y
Biorad 3	38	2.65	5.0		5.5		0.65	Y	Y
UMMC									
MORE 1	40	0.010		0.0016		0.0015		Y	N/A
MORE 2	40	0.88	3.1		5.7		0.002	Y	Y
MORE 3	40	13.82	2.1		3.2		0.04	Y	Y
ARUP									
MORE 1	62	0.010		0.0032		0.0026		Y	N/A
MORE 2	62	0.996	4.4		4.7		0.78	Y	Y
MORE 3	62	14.6	3.6		3.4		0.54	Y	Y
SBMF									
MORE 1	40	0.01		0.0045		0.0040		Y	N/A
MORE 2	40	0.962	6.0		6.5		0.74	Y	Y
MORE 3	41	14.34	4.5		5.5		0.25	Y	Y
QUES									
MORE 1	40	0.017		0.0022		0.0012		Y	N/A
MORE 2	39	0.948	1.9		2.4		0.17	Y	Y
MORE 3	40	13.9	2.1		2.3		0.66	Y	Y
EMOR									
MORE 1	36	0.01		0.0035		0.0027		Y	N/A
MORE 2	36	0.98	6.0		6.2		0.90	Y	Y
MORE 3	36	14.85	8.2		8.1		0.71	Y	Y

Conclusion: The acceptance criteria were met for assay precision for results adjusted with the thermal algorithm at all external laboratory sites.

10.4. Overall Conclusion– Field Effectiveness Study

The results of these studies demonstrate that the AccuTnI assay with the thermal algorithm on the Access 2 instrument can be used effectively under expected field conditions in the clinical laboratory.

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Section 11.0

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11.0 Proposed Labeling

Copies of the following proposed labels are provided in Appendix 31:

- Reagent package labels
- Calibrator package
- Reagent product insert
- Access 2 Immunoassay IFU

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Section 12.0

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12.0 Overall Conclusion

The information provided in this document demonstrates that the proposed new device, the Access AccuTnI assay, has the same intended use as the predicate device. Moreover, the Access 2 instrument, which was modified to address thermal sensitivity, has the same intended use as the predicate device. In addition, verification and validation testing, the clinical and analytical data, the clinical use of the product reflected in current MI diagnostic guidelines, and other scientific information provided in this submission demonstrate that the Access AccuTnI assay on the Access 2 Immunoassay Systems is as safe and effective as the predicate devices. Taken together, this information establishes the substantial equivalence of Beckman Coulter's products to predicates.

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Section 13.0

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13.0 CLIA Request

A formal CLIA request is provided in the following pages.

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U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: CLIA Categorization Request

Dear Madam/Sir:

Beckman Coulter Inc. is submitting the attached documentation to request a CLIA complexity categorization for the Access AccuTnI assay based on 42 CFR 493.17 of the CLIA 1988 regulation.

A description of the product is provided, in addition to the draft Instructions for Use. Three copies are provided.

Please review this request and contact me if you have any questions.

Sincerely,

Valynda L. Machen, CQA, RAC (US)
Group Manager Regulatory Affairs
Phone: (952) 368-1383
Fax: (952) 368-7610
vmachen@beckman.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Request for Complexity Categorization

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

The Access 2 was cleared (K922823/A007) July 2, 2001.

Evaluation in accordance with 42 CFR 493.17 (Test Categorization):

A complexity categorization scoring was performed on the Access AccuTnI assay. The results of the scoring appear in the table below. The categorization was based on the specific criteria outlined in 42 CFR 493.17 of the CLIA 1988 regulation. Using those criteria, all seven sections were assigned scores from 1 to 3, with 1 indicating the lowest level of complexity. The Access AccuTnI assay was determined to be moderately complex, having a total score of less than 12 points.

The rating of moderately complex assays is based on the rationale contained in the regulation. For this assay, the analyst needs minimal scientific and technical knowledge beyond the step-by-step directions, which may be obtained through on-the-job instruction, to properly perform the assay procedures and report results (1 point). The analyst needs minimal training and experience for the preanalytic,

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analytic, and postanalytic phases of the testing process to perform the assay (1 point). The Access AccuTnI assay is liquid, prepackaged, premeasured, and requires no preparation (1 point). The Access 2 Immunoassay System has automatic specimen processing, computer controlled timing steps, built-in function checks, and no required calculations, necessitating only periodic calibration by the analyst at the request of the software system (1 point). Calibration and control materials are readily available, stable, and easily incorporated into the procedure. Proficiency testing materials are available and stable (1 point). Troubleshooting is clearly described in instrument manuals and maintenance steps can be easily performed with appropriate training (1 point). Minimal interpretation and judgment is required on the part of the analyst as decision making is not required through the testing process itself (1 point).

Table 1: Access AccuTnI Assay Test Complexity Assessment

Category	Access AccuTnI Assay
Knowledge	1
Training	1
Reagent Preparation	1
Operational Steps	1
QC/PT Materials Availability/Stability	1
Troubleshooting & Maintenance	1
Judgment	1
Total	7
Interpretation	**Moderately complex**

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Appendix 1: Risk Management Scoring Criteria

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Risk Management Scoring Criteria from Beckman Coulter Corporate Procedure, BCCP0083

Table 1: Severity of Harm Rankings

Severity of Harm		Definition	Severity of Harm	Definition
		Potential harm to patient / operator / service personnel		**Potential damage to property/ equipment / environment**
5	**Life-threatening Injury**	Injury that could lead to death.	**Catastrophic Damage**	Potential for a fire or other property damage that could lead to death or a life-threatening injury; extensive, irreparable environmental damage.
4	**Permanent Injury**	Irreversible impairment of a body function or irreversible damage to a body structure, including any injury that would require medical or surgical intervention to preclude irreversible impairment or damage.	**Serious Damage**	Facility/equipment damage that could cause long-term closure of a medical facility; irreparable damage to the environment; substantial noncompliance with occupational health, safety or environmental laws or regulations.
3	**Medically Reversible Injury**	Bodily impairment or damage that can be reversed by medical or surgical intervention. Note: Injuries requiring intervention to preclude irreversible impairment or damage are classified as Permanent Injury.	**Major Damage**	Damage that could cause short term closure of a medical facility (e.g. due to contamination) or need to replace an IVD instrument; environmental damage that is reversible only with professional remediation.
2	**Temporary Injury**	Temporary impairment or damage that is reversible without medical or surgical intervention.	**Minor Damage**	Damage that would not cause closure of a facility or loss of an IVD instrument, but might require repair; environmental damage that is reversible without remediation.
1	**Negligible Injury**	Minor or transient medical complaint that would be considered no more than a nuisance or inconvenience.	**Negligible Damage**	No discernible impact on facilities, equipment, or the environment.

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Table 2: Probability Rankings

Probability of Occurrence		Definition (Applies to P_1, P_2 and P_{Total})
5	Highly Likely	The event is expected to occur at a high rate.
4	Frequent	The event is expected to occur often.
3	Occasional	The event is expected to occur sometimes.
2	Remote	The event is not expected to occur, but could occur in rare situations.
1	Highly Unlikely	The event is not expected to occur based on current knowledge.

Table 3: Probability of Harm

P_1 (Probability of a hazardous situation)	P_2 (Probability of harm from a hazardous situation)	P_{Total} (Probability of Harm*)
Highly Likely	Highly Likely	Highly Likely
	Frequent	Frequent
	Occasional	Occasional
	Remote	Remote
	Highly Unlikely	Highly Unlikely
Frequent	Highly Likely	Frequent
	Frequent	Frequent
	Occasional	Occasional
	Remote	Remote
	Highly Unlikely	Highly Unlikely
Occasional	Highly Likely	Occasional
	Frequent	Occasional
	Occasional	Occasional
	Remote	Remote
	Highly Unlikely	Highly Unlikely
Remote	Highly Likely	Remote
	Frequent	Remote
	Occasional	Remote
	Remote	Remote
	Highly Unlikely	Highly Unlikely
Highly Unlikely	Highly Likely	Highly Unlikely
	Frequent	Highly Unlikely
	Occasional	Highly Unlikely
	Remote	Highly Unlikely
	Highly Unlikely	Highly Unlikely

* The correct P_{Total} is the lower probability of P_1 and P_2.

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Table 4: Risk Acceptability Matrix

Patients and Users		Severity of Harm				
		Negligible Injury	Temporary Injury	Medically Reversible Injury	Permanent Injury	Life Threatening Injury
Property or Environment		Negligible Damage	Minor Damage	Major Damage	Serious Damage	Catastrophic Damage
Probability of Harm (P_{Total})	Highly Likely	II	III	III	III	III
	Frequent	II	II	III	III	III
	Occasional	I	II	II	III	III
	Remote	I	I	II	II	III
	Highly Unlikely	I	I	I	II	II

Table 5: Risk Acceptability Matrix Key

Zone	Acceptability Description
III	Unacceptable: Risks that fall in this zone cannot be accepted without a risk/benefit analysis and management approval.
II	Acceptable risk, if as low as reasonably practicable (ALARP). Risks in this zone will be investigated for the feasibility of risk reduction, and risk control measures are required unless rationale is provided to substantiate that further risk reduction is not feasible.
I	Acceptable: Risks that fall in this zone are low and do not require further risk control.

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Appendix 2

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Appendix 2: Access 2 3.3 Work Item Risk Assessment

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Totally Committed to Quality

Access 2 3.3 Work Item Risk Assessment

My electronic signature confirms my approval of this document for its intended use.

APPROVALS:	APPROVED ON (MM/DD/YYYY):
Shipe, Brian M	08/24/2011 09:15:38 (PDT)
Flohr, Nicole C	08/24/2011 09:17:51 (PDT)
Marchant, Jean M	08/24/2011 09:21:50 (PDT)
Weber, Chad M	08/24/2011 10:57:52 (PDT)
Auradon, Francois B	08/24/2011 12:17:44 (PDT)
Lowe, David E	08/26/2011 04:58:36 (PDT)

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Table of Contents

Table of Contents 2
Access 2 3.3 Work Item Risk Assessment Overview 2
Overview 2
References 2
Approvers 2
Table of Figures 2
Access 2 3.3 Work Item Risk Assessment 3
Revision History 5

Access 2 3.3 Work Item Risk Assessment Overview

Overview

This document contains the risk assessment for individual work items associated with the thermal correction of test results. The work items listed below all contain a concern code *A* or PMN code *B* and were implemented in the Access 2 v3.3. Risk assessments for other work items are contained in the work item itself.

References

Document	Location
BCCP0083	EDMS: Search for "BCCP0083"
BCCP0109	EDMS: Search for "BCCP0109"
NexStep Data Reduction Requirements	EDMS: Cabinets / Diagnostics Development / IDC / Projects / Access 2 / Access 2 Console Software / Access 2 Requirements
Thermal Dose Correction Design	EDMS: Cabinets / Diagnostics Development / IDC / Projects / NexGen Access / NexGen Console Software / Design docs

Approvers

At a minimum, the following people are required to approve this document:

- Access 2 software development team leader
- Access 2 software verification/validation team leader
- Access 2 console development expert
- Access 2 instrument development expert
- Access 2 software verification/validation expert

Table of Figures

Table 1: Access 2 3.3 Work Item Risk Assessment 3

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Access 2 3.3 Work Item Risk Assessment

Table 1: Access 2 3.3 Work Item Risk Assessment

ID	Item Name / Function / Process Step	Software Requirement	Failure Mode (Cause of Hazard)	Failure Cause	System Effect (Hazard)	End Effect (Hazardous Situation)	Severity of Harm (S)	Pre-Mitigation OCC	Pre-Mitigation P_1	Pre-Mitigation Risk	Mitigation (Risk Control Measures)	Post-Mitigation OCC	Post-Mitigation P_1	Post-Mitigation Risk
1	Work Item #36085: Merge Calibration and Result Temperature Calculation from Del	System Temperature Requirements: REQ36 Result Temperature Requirements: REQ37, REQ38, REQ38.1, REQ38.2, REQ39, REQ40, REQ40.1, REQ40.2, REQ40.3, REQ40.4, REQ40.5 Curve Temperature Requirements: REQ41, REQ42, REQ43, REQ43.1, REQ43.2, REQ45, REQ46, REQ46.1, REQ46.2	The system software has insufficient valid data to calculate a temperature for an individual test result or calibration curve.	No temperature data points are associated with either a test result or calibration curve due to an implementation error.	The calculated temperature for the test result or calibration curve will not be available for result calculation.	• Test result is unavailable to physician. • Result may be delayed as test is rerun. • Delay to patient results caused by re-running calibrations or troubleshooting software errors.	Permanent Injury (4)	Occasional (3)	Remote (2)	II	• The result shall be suppressed from the user if no temperature data points are associated with the result. • The calibration curve shall be suppressed from the user and shall not be used in test result calculations if no temperature data points are associated with the calibration curve. • Add extra verification to ensure temperature data points are properly recorded and associated with individual test results.	Highly Unlikely (1)	Highly Unlikely (1)	I
				Mathematical failure (e.g. divide by zero) due to an implementation failure.	Mathematical failures (e.g. divide by zero) may cause software crashes or errors.		Permanent Injury (4)	Occasional (3)	Remote (2)	II	• A high precision, floating point number representation is used to ensure that mathematical calculations are performed correctly. o The use of the C++ variable type *double* on an Intel x86 processor allows for precision up to 1.0×10^{-308} or for numbers as large as 1.0×10^{308}. • Add additional error handling to detect mathematical calculation failures. • If an error does occur, affected test results and calibration curves shall be suppressed from the user.	Highly Unlikely (1)	Highly Unlikely (1)	I
			The system software incorrectly calculates the temperature for an individual test result or calibration curve.	Incorrect implementation of mathematical functionality.	Incorrectly calculated result temperatures will be used in downstream calculations of the test results, affecting the final dose value. Incorrectly calculated calibration curve temperature will be used in downstream calculations of any test results calculated against the curve, affecting the final dose values of those test results.	• Incorrectly calculated test result or calibration temperatures may lead to generating erroneous, but believable test results. • Incorrect temperature data could be used as part of internal research or development efforts to classify the thermal sensitivity of new or existing assays.	Life-threatening Injury (5)	Occasional (3)	Remote (2)	III	• Leverage existing mathematical libraries to perform the temperature calculation whenever possible. These libraries have been exercised internally and in the field without reported failures. Reuse libraries for calculations on both test results and calibration curves to prevent adding defects by duplicating functionality. • A high precision, floating point number representation is used to ensure that mathematical calculations are performed correctly. o The use of the C++ variable type *double* on an Intel x86 processor allows for precision up to 1.0×10^{-308} or for numbers as large as 1.0×10^{308}. • Add the ability to run unit tests against the mathematical calculation. This allows for testing complicated mathematical calculations very quickly and verifying the calculation provides correct answers. The unit tests may be rerun after updates have been made to the mathematical libraries. The unit tests will detect if any of the changes introduced any defects. o Unit test code has been inspected and tested as part of the normal software development process.	Highly Unlikely (1)	Highly Unlikely (1)	II
				Incorrect method was used for calculating a temperature for the test result or calibration curve due to improper implementation			Life-threatening Injury (5)	Occasional (3)	Remote (2)	III	• Add extra verification to ensure the temperature calculation method is loaded from the API into the database and the data reduction sequence determines the correct temperature calculation method from the database.	Highly Unlikely (1)	Highly Unlikely (1)	II
			The system software does not detect that a test result temperature does not meet specifications.	An individual temperature data point that is out of the instrument's temperature range is not detected due to improper implementation.	The system software allows the affected test results to be processed and generates results for the user, even though the affected tests were run in conditions outside the instrument's specifications.	The result reported to the user may be incorrect since the assay was not validated in the temperature range the test was run in.	Life-threatening Injury (5)	Occasional (3)	Remote (2)	III	• Leverage existing mathematical libraries to perform the temperature calculation whenever possible. • A high precision, floating point number representation is used to ensure that mathematical calculations are performed correctly. o The use of the C++ variable type *double* on an Intel x86 processor allows for precision up to 1.0×10^{-308} or for numbers as large as 1.0×10^{308}. • Add the ability to run unit tests against the mathematical calculation. This allows for testing complicated mathematical calculations very quickly and verifying the calculation provides correct answers. The unit tests may be rerun after updates have been made to the mathematical libraries. The unit tests will detect if any of the changes introduced any defects. • Include additional software developers in the code inspection to look for defects.	Highly Unlikely (1)	Highly Unlikely (1)	II
				Calculation of the range of temperature data points associated with the test result is incorrect due to improper implementation.			Life-threatening Injury (5)	Occasional (3)	Remote (2)	III		Highly Unlikely (1)	Highly Unlikely (1)	II
			The system software does not detect that a calibration curve temperature does not meet specifications.	Calculation of the range of temperature data points associated with the calibration curve is incorrect due to improper implementation.	The calibration curve that was run outside the instrument's specifications is not cancelled and future patient samples may be run against the curve.	The calibration curve being used to calculate results may be incorrect since the assay was not validated in the temperature range the curve was run in, leading to the possibility of erroneous, but believable test results.	Life-threatening Injury (5)	Occasional (3)	Remote (2)	III	• Leverage existing mathematical libraries to perform the temperature calculation whenever possible. • A high precision, floating point number representation is used to ensure that mathematical calculations are performed correctly. o The use of the C++ variable type *double* on an Intel x86 processor allows for precision up to 1.0×10^{-308} or for numbers as large as 1.0×10^{308}. • Add the ability to run unit tests against the mathematical calculation. This allows for testing complicated mathematical calculations very quickly and verifying the calculation provides correct answers. The unit tests may be rerun after updates have been made to the mathematical libraries. The unit tests will detect if any of the changes introduced any defects. • Include additional software developers in the code inspection to look for defects.	Highly Unlikely (1)	Highly Unlikely (1)	II

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2	Work Item 856089: Update the Access 2 Expression Parser to Support the Temperature Correction Algorithm	Expression Parser Requirements: REQ57, REQ58, REQ58.1, REQ58.2, REQ58.9, REQ64, REQ64.1, REQ64.2, REQ64.9 Expression Parser Calculation Timing Requirements: REQ51, REQ51.1, REQ51.2 Expression Parser Error Condition Requirements: REQ65.1, REQ65.2, REQ65.3	Evaluation of the thermal expression produces the wrong quantitative result	Incorrect evaluation of the mathematical expression due to incorrect implementation (e.g. order of operations (PEMDAS), operator mathematics not properly implemented, etc...).	The wrong quantitative result is used for qualitative analysis (e.g. result flagging or qualitative interpretations) and is incorrectly reported to the user.	The test result reported to the user may be incorrect, leading to erroneous but believable test results.	Life-threatening Injury (5)	Occasional (3)	Remote (2)	III	• Leverage the existing expression parser which is currently used in the system software for evaluation of derived results and reflex conditions. ○ The expression parser has been fully verified and validated and has been used without reported mathematical failures. ○ The expression parser uses a high precision, floating point number representation to ensure that mathematical calculations are performed correctly. ○ Reuse of the expression parser for the thermal adjustment evaluation reduces duplicated code and the chances of injecting defects. ○ Modifications to the expression parser are limited to the section that parses an expression to look for thermal adjustment keywords and replace with the keywords with their numeric values (e.g. "RESULT_TEMP" is replaced with the calculated result temperature). ○ No updates are required in the expression parser to evaluate the parsed thermal adjustment expression. • Include additional software developers in the code inspection to look for defects	Highly Unlikely (1)	Highly Unlikely (1)	II
			Evaluation of the thermal expression produces an invalid mathematical operation (e.g. divide by zero, square root of a negative number, etc...).	Thermal expression contains a mathematical error due to improper thermal expression design (not a software defect, e.g. thermal expression contains "RAW_DOSE / 0").	The system software would crash, preventing processing of new samples and generating test results until the system software was restarted	• Test result is unavailable to physician • Result may be delayed at least is rerun. • Delay to patient results caused by re-running calibrations or troubleshooting software errors.	Permanent Injury (4)	Occasional (3)	Remote (2)	II	• Leverage the existing expression parser which is currently used in the system software for evaluation of derived results and reflex conditions. ○ The expression parser already contains additional error handling to detect mathematical calculation failures. ○ The expression parser uses a high precision, floating point number representation to ensure that mathematical calculations are performed correctly. • A test result shall be suppressed from the user if the thermal expression is unable to be evaluated. • Verification of the thermal adjustment expression near boundary conditions of different input values ensures that the expression itself or the input values will not cause invalid mathematical operations to occur. • Verify the thermal adjustment expression operates appropriately nearly clinically significant boundary conditions for different expression inputs.	Highly Unlikely (1)	Highly Unlikely (1)	I
				Calculated values cause an error in the calculation of the expression (e.g. the calculated calibration temperature is 0.0 and thermal expression contains RESULT_TEMP / CAL_TEMP).			Permanent Injury (4)	Occasional (3)	Remote (2)	II		Highly Unlikely (1)	Highly Unlikely (1)	I
3	Work Item 856090: Merge Dose Correction–Calculate and display temperature-corrected dose	Result Correction and Calculation Requirements: REQ32, REQ47, REQ48, REQ49, REQ50, REQ51, REQ52, REQ53, REQ63 Intermediate Value Data Storage Requirements: REQ62, REQ62.1, REQ62.2, REQ62.3, REQ62.4, REQ62.9 Result Calculation Error Condition Requirements: REQ63	The wrong value in the data reduction sequence is thermally adjusted (e.g. adjust RLU value instead of quantitative dose or application of an off board dilution factor before thermally adjusting the dose).	Incorrect design of thermal adjustment in the data reduction sequence.	The wrong quantitative result is used for qualitative analysis (e.g. result flagging or qualitative interpretations) and is incorrectly reported to the user.	The test result reported to the user may be incorrect, leading to erroneous but believable test results.	Life-threatening Injury (5)	Occasional (3)	Remote (2)	III	• Reviewed the design of quantitative, semi-quantitative and qualitative assay data reduction sequence with the thermal modeling team to determine the correct value to thermally adjust. ○ Ensures the thermal adjustment expression is evaluated at the correct location in the data reduction sequence and thermally adjusts the correct value. • See *Thermal Adjustment Design* for the design that describes the updates to the data reduction sequence.	Highly Unlikely (1)	Highly Unlikely (1)	II

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Revision History

Version	Initials	Date	Summary of Changes
1.0	BMS	08/24/2011	Initial version.

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Appendix 3

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Appendix 3: Access 2 3.3 System Software Change Risk Assessment

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Totally Committed to Quality

Access 2 3.3
System Software Change Risk Assessment

My electronic signature confirms my approval of this document.

APPROVALS: (MM/DD/YYYY):	APPROVED ON
Frandsen, Gordon	03/21/2012 07:01:25 (PDT)
Peterson, Ursula I	03/21/2012 07:23:56 (PDT)
Severson, Ryan M	03/21/2012 08:07:53 (PDT)
Roberts, Sean M	03/21/2012 08:34:11 (PDT)
Auradon, Francois B	03/21/2012 10:50:06 (PDT)
Matzke, Scott D	03/22/2012 08:27:49 (PDT)
Guimond, Suzanne R	03/22/2012 13:12:19 (PDT)

Version:
1.20, CURRENT

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Table of Contents

1. OVERVIEW 3

1.1. PURPOSE 3
1.2. BACKGROUND 3
1.3. REFERENCES 3
1.4. DEFINITIONS 4
1.5. REVISION HISTORY 4

2. RISK ASSESSMENT 6

2.1. RISK ASSESSMENT WORKSHEET 6
2.2. RISK CONTROL MEASURES 6
2.3. WORK ITEMS WITH A "HIGH" CONCERN CODE 6
2.4. RISK ASSESSMENT CONSIDERATIONS 6
2.5. ADDITIONAL COLUMNS NOT IN BCCP0109 7
2.6. SAFETY FMEA TABLES 8
2.6.1. System Software SFMEA 8
2.6.2. Issues identified in currently fielded software 13
2.6.3. Issues introduced during this release cycle 14
2.7. RISK CONTROL MEASURES RESULTS 17
2.8. ACCEPTABILITY RATIONALE 17
2.9. RISK ASSESSMENT CONCLUSION 18

APPENDIX A 19

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

1. Overview

1.1. Purpose

This Risk Assessment documents the risk evaluation of implementing the changes listed in the Access 2 3.3 Work Item Inclusion List. Verification and validation activities are identified for each change or set of changes. The verification and validation degree of rigor is commensurate with the risk level of the change.

This document also:

- Provides the analysis driving the risk mitigations and confirms the acceptability of the residual risks.
- Determines which changes need to be communicated to Development and Manufacturing contractors.
- Determines which changes might affect internal systems that interact with the Access 2 instrument.

1.2. Background

Software version 3.3 contains the following software corrections and enhancements:

- Thermal dose correction
- New Assay command (U) to include Frequency lock during mixing

1.3. References

Document	EDMS Object Name
Software Development Plan	Access 2 3.3 Software Development Plan
Access 2 3.3 Software Risk Management Plan	Access 2 3.3 Software Risk Management Plan
Interim Controls	Policy 0038
Access 2 3.3 work Item inclusion List	Access 2 3.3 work Item inclusion List
Access 2 3.3 Work Item Risk Assessment	Access 2 3.3 Work Item Risk Assessment
NexStep Glossary	NexStep Glossary
BCCP0085 Software Development	BCCP0085
BCCP0082 Product Safety Risk Management	BCCP0082
BCCP0083 Risk Acceptability	BCCP0083
BCCP0109 Risk Analysis Methods	BCCP0109
BCCR0001 Lexicon	BCCR0001
AccuTnI Product Severity Reference	AccuTnI PSR
Rubella IgM Product Severity Reference	Rubella IgM Product Safety Reference
Toxo IgM Product Severity Reference	Toxo IgM II Product Safety Reference
Access 2 3.3 PLRA WI 96487	Access 2 3.3 PLRA WI 96487
Access 2 3.3 PLRA WI 133838	Access 2 3.3 PLRA WI 133838

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Document	EDMS Object Name
Access 2 3.3 PLRA WI 133840	Access 2 3.3 PLRA WI 133840
Access 2 3.3 PLRA WI 134632	Access 2 3.3 PLRA WI 134632
Access 2 3.3 PLRA WI 134656	Access 2 3.3 PLRA WI 134656
Access 2 3.3 PLRA WI 169583	Access 2 3.3 PLRA WI 169583
Access 2 3.3 PLRA - Temp Point Collection	Access 2 3.3 PLRA - Temp Point Collection

1.4. Definitions

ALARP	As Low As Reasonably Practicable
Change Point Analysis	Technical Peer Review held for the software build to analyze the changes introduced into the software build and the Impact of these changes on scheduled verification activities.
Concern Code	Indicates the depth of detail required for the Hazard analysis A – High, B – Moderate, C – Low, D – Minor, E – None (See Access 2 3.3 Software Development Plan for complete definitions)
DCTD	Diagnostic Copy To Disk
LIS	Laboratory Information System
PLRA	Post Launch Risk Assessment
PSR	Product Safety Reference
SFMEA	Safety Failure Modes Effects & Analysis
TFS	Team Foundation Server
WI	Work Item

1.5. Revision History

Version	Date	Initiator	Description of Change
1.0	07/19/2011	FBA	Initial revision.
1.1	07/28/2011	FBA	Include independent reviewer comments.
1.2	08/01/2011	FBA	Corrected Background (§1.2)
1.3	08/09/2011	FBA	Update after review with regulatory Reorganized and clarified sections please see tracked changes.
1.4	08/09/2011	FBA	Added U command to Background.

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1.5	08/17/2011	FBA	Update to include comments from independent reviewer. Added Section 2.5 "Additional Columns...." Re-worded sections: 2.3 "Work Items with a ...", 2.4 "risk assessment considerations", 2.8 "Acceptability Rationale", 2.9 "Conclusion"
1.6	10/24/2011	GF	Added WI #s for Help string updates.
1.7	10/24/2011	GF	Added WI #s for consolidated NT/XP, added row 15 for Help and string updates.
1.8	10/31/2011	GF	Update WI #s for consolidated NT/XP and installation.
1.9	11/14/2011	GF/FBA	Update with addition of message lockup issue.
1.10	11/17/2001	GF	Add clarification to System Effect on row 14 per 3rd party review comment. Attach IC-1 form.
1.11	11/23/2001	GF	Clarification of section 2.6 item #16. Add result of risk control measures in section 2.7.
1.12	11/23/2001	GF	Attach IC-1 form.
1.13	01/27/2012	FBA/GF/DL	Added Work Items found during test §2.6.2 and §2.6.3
1.14	02/17/2012	RW/GF	Added system level protocol to table 2.6.1 row 9 and section 2.8.
1.15	03/1/2012	GF	Populated tables for PLRAs and SFMEAs §2.6.2 and §2.6.3.
1.16	03/12/2012	FBA/GF/DEL	Updated document with latest Work Items.
1.17	03/13/2012	GF/FBA	Incorporate third party review comments
1.18	03/15/2012	GF	Add PLRAs and Lexicon to References. Attach IC-1 form.
1.19	03/16/2012	GF	Add PSR selection method to §2.6. Add PSR references to §1.3.
1.20	03/20/2012	GF	Add 2 Systems Integration Protocols to row 6 of §2.6.1.

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2. Risk assessment

2.1. Risk Assessment Worksheet

The Safety FMEA table groups work items by areas of change and evaluates the risk of each combined change groups. Individual work items with a high level of concern are discussed in section "Work Items with a Concern Code A".
Note: the Work Item numbers placed in parenthesis are work items for which no code was changed and thus present no risk.

2.2. Risk Control Measures

The Access 2 3.3 Software Development Plan (section 6.1) requires that all identified risks are mitigated through design.
The level of attention for each is commensurate to the concern code for each Work Item.
In addition for each Software Change Work Item the following will be reviewed:

- Root cause analysis (defects only).
- Requirements.
- Changes to the design.
- Code Changes.
- Hazard analysis
- Impact analysis.
- Unit tests.
- Release notes.
- Test cases for verification.

Each work item will be verified to ensure the design meets the intent of the Additional Testing may be prescribed to increase the confidence level and to ensure completeness of design mitigation.

2.3. Work Items with a "High" Concern Code

Concern Code "High" (Concern Code A) risk assessments are in a separate file "Access 2 3.3 Work Item Risk Assessment.docx" in EDMS. These risk assessments are focused on individual Work Items with a high level of concern.

2.4. Risk Assessment considerations

Post-Mitigation scoring is assessed before performing the actual prescribed testing for the following reasons:

- First these tests will not be complete unless they all pass (ie: software changes will be iterated until the prescribed test is successful). The post mitigation scoring reflects a passing test.
- Second Post-Mitigation risk is needed in order to evaluate the necessity for additional design mitigation, additional testing or risk management activities.

This approach allows for proactive mitigation of any unacceptable risk. If necessary, an iterative risk assessment process will be used until all risks are acceptable.

Because the risk analysis's intent is to encompass all assays available on the Access 2 platform, a worst case severity will be used. Subsequently, a severity of Life-threatening Injury will be used in cases where a wrong result is identified as a hazardous situation. For instances where a delay in result is identified as

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the hazardous situation, a severity of Permanent Injury will be used. Both worst case severities are derived from Rubella IgM or Toxo IgM (wrong result), and AccuTnI (delay in result) PSRs

2.5. Additional columns not in BCCP0109

Two columns were added to the BCCP0109 template to capture impact of changes to assay processing and identify the need to initiate the contract developers and contract manufacturers notification process

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2.6. Safety FMEA tables

2.6.1. System Software SFMEA

ID	Item Name/ Function/ Process Step	Software requirement	Failure Mode (Cause of Hazard)	Failure Cause	System Effect (Hazard)	End Effect (Hazardous Situation)	Severity of Harm (S)	Existing In-place controls	Pre-Mitigation OCC	Pre-Mitigation P1	Pre-Mitigation Risk	Mitigation (Risk Control Measures)	Impacts assay processing?	Contractor Notification?	Post-Mitigation OCC	Post-Mitigation P1	Post-Mitigation Risk
1.	Temperature monitoring Work Items: 35077, 35078, 36080, , 37171, 79685, 82433, 96421	Requirements listed in Thermal Software Requirements document. REQ 1, REQ 1.1, REQ 1.1.1, REQ 1.1.2, REQ 1.2, REQ 2, REQ 3, REQ 8, REQ 8.1	Monitored temperature values are not accurate.	Temperature calculation formula is incorrectly implemented.	Thermally corrected result dose is incorrectly calculated based on erroneous temperature input data.	Physician receives incorrect test results	Life-threatening Injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone III (Unacceptable)	- Prescribed verification: Perform Temperature Monitoring and Assigned Temperature Detection protocol to verify the integrity of the temperature monitoring implementation.	N	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
			Temperature monitoring is not available	Temperature acquisition circuit is faulty.	Unable to calculate adjusted dose for Thermally corrected assay.					Remote	Risk Zone II (ALARP)		N	N			
2.	Diagnostic Copy to Disk for Thermal Data Work Item 36091	Requirements listed in Thermal Software Requirements document REQ 7.4, REQ 9, REQ 9.1, REQ 9.2, REQ 9.3, REQ 9.4, REQ 9.5, REQ 9.6.	Incorrect or no data saved in the Copy to Disk File	Faulty implementation	None, the Copy to Disk file is used for troubleshooting only	None, the Copy to Disk file is used for troubleshooting only No impact to Patient Safety.	Negligible Damage	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone I (Acceptable)	- Prescribed verification: Perform Test case Work Item 84562 to verify that the contents of the DCTD files are correct. 09001243 Dec07 ca	N	Y	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable

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3.	Simulate specific replicate temperature information Work Item 84557, 36082	Work item specific requirement listed in the work items.	Simulation is not working as expected.	Faulty implementation	None, the simulation is used for development and test only	None, the simulation is used for development and test only No Impact to Patient Safety.	Negligible Damage	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone I	- Analysis performed in the change point analysis and risk and hazard section of the WIs indicate no additional verification other than the test case specified in the test tab of the work item is necessary.	N	N	Highly unlikely	Highly unlikely	Risk Zone I
4.	Assigned Temperature Determination Work Item: 36085, 36090, 96472	Requirements listed in Thermal Software Requirements document. REQ4, REQ5, REQ6, REQ6.1, REQ6.1.1, REQ6.1.2, REQ6.1.3 ,	Temperature calculation is erroneous	Incorrect requirements or design or faulty implementation	Thermally corrected result dose is incorrectly calculated based on erroneous temperature assignment .	Physician receives incorrect patient test results	Life-threatening injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- **Prescribed verification:** Perform Temperature Monitoring and Assigned Temperature Detection protocol to verify the integrity of the temperature monitoring implementation.	Y	Y	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
5.	Data storage Work Item 82772	Requirements listed in Thermal Software Requirements document. REQ3, REQ9, REQ9.1,REQ 9.2, REQ9.3, REQ9.4, REQ9.5, REQ9.6, REQ9.7	Incorrect data stored in the Database	faulty implementation , database corruption.	System unable to access Thermal data	System unable to calculate or report test results, Delay in reporting patient test results to Physician	Permanent injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- **Prescribed verification:** Perform Data Storage protocol to verify the integrity of the Thermal data retention implementation.	N	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)

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6.	Algorithm Implementation Work Items: 36089, 36090, 96754	Requirements listed in Thermal Software Requirements document. REQ4, REQ4.1, REQ5, REQ5.1, REQ6, REQ6.2, REQ6.1, REQ6.1.1, REQ6.1.2, REQ6.1.3, REQ14, REQ14.1, REQ14.2	No correction or incorrect adjusted dose.	Incorrect requirements or design or faulty implementation	Incorrect patient test results generated	Physician receives incorrect patient test results	Life-threatening injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Prescribed verification: Perform Test Result Reporting protocol to verify the integrity of the temperature monitoring implementation. Perform "Access 2 3.3 Systems Integration Software Testing Protocol" and "Access 2 IVD 3.3 Systems Integration Software Testing Protocol" using live assay results and real time temperature data to verify that the software implementation is correct.	Y	Y	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
7.	New thermal APF implementation Work Items: 68601	Requirements listed in Thermal Software Requirements document. REQ6, REQ10, REQ15, REQ15.1	APF data improperly managed in the System	Incorrect requirements or design or faulty implementation	Incorrect patient test results generated.	Physician receives incorrect patient test results	Life-threatening injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Prescribed verification: Perform Test Result Reporting protocol to verify the integrity of the temperature monitoring implementation.	N	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
8.	Load Thermal APF Work Items: 82760, 36092, 96760	Requirements listed in Thermal Software Requirements document. REQ10, REQ16, REQ16.1, REQ16.2, REQ16.3	System cannot load APF.	Incorrect requirements or design or faulty implementation	Unable to operate system	Delayed in reporting patient test results to Physician. Requires a call to hotline.	Permanent injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Analysis performed in the change point analysis and risk and hazard section of the WIs indicate no additional verification other than the test case specified in the test tab of the work item is necessary.	N	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)

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9.	Database watch mechanism Corrupts Test State of Results While Being Calculated Work Item: 96309	Requirements listed in NexGen Data Reduction Requirements REQ7 Detailed Work Item Requirements Result state is set to TS_COMPLETED after the result has been successfully calculated.	Samples appear as "Aspirated" in the sample manager dialog after the run has been completed and the instrument is in ready mode.	Samples are improperly marked as aspirated when they should be marked as completed.	Thermal correction is not applied on the recalculation since there is a check to prevent the instrument from thermally correcting the result multiple times	Incorrect patient test results reported to the Physician If a thermal correction is required, however, the patient test result will be correct if no thermal correction is required	Life-threatening injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Analysis performed in the change point analysis and risk and hazard section of the WIs indicate no additional verification other than the test case specified in the test tab of the work item is necessary.	N	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
10.	Interactions between changes and the sum total of all changes in this release	No existing requirement.	Individual changes conflict with each other	Conflicts between Individual changes not analyzed	None Identified	None	N/A	N/A	N/A	N/A	N/A	- Prescribed verification: Validation of the system software operation performance and its ability to meet the user indicates the need for the execution of the "NexStep Integration Test Procedure." Testing performed during validation will confirm broad-based system functionality. This includes the "Access 2 3.3 Software System Level Test Protocol" using wet assay processing to increase confidence that the cumulative set of changes have not negatively impacted system level functionality and performance. Execution of the Selected Access 2 3.3 Installation scenarios from "Install Test Procedure" will mitigate process risks of producing a new system software build and production of the gold master CD. The remainder of the Access 2 test procedures do not require re-execution because functionality verified by those procedures was determined to be unaffected by the WIs reviewed in the change point analysis.	Y	N	N/A	N/A	N/A

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11.	Interactions with ADAM	ADAM requirements In EDMS	Changes to the Copy to Disk files are not compatible with the ADAM application	New data in saved files Conflicts with ADAM functionality	Unable to gather production and development data from Dxl	Reagent production must revert to a manual system to verify the data. No impact to Patient Safety.	Negligible damage	None. ADAM used in house only.	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable)	ADAM is being revised simultaneously and will be fully tested as part of the ADAM development.	N	Y	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable)
12.	Change in the final algorithm	Requirements listed in Thermal Software Requirements document.	Changes to the Algorithm following system software verification.	Assay development changes to the algorithm	System software handling of new algorithm may produce erroneous patient test results generated.	Physician receives incorrect patient test results	Life-threatening injury	Development activities for the new algorithm will ensure that it can be run.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Prescribed verification: Re-execute test cases related to result and algorithm either standalone test case WI or test cases embedded in an implementation WI.	N	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
13.	New pipetting command for mixing with VCO lock Work Item: 80778	Work Item specific requirement listed in the work items.	Mixing not performed correctly.	Faulty implementation	Incorrect patient test results generated	Physician receives incorrect patient test results	Life-threatening injury	- Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Perform appropriate verification and validation of the new U command prior to implementation for release. Reference validation summary in Software Testing and Software Validation Summary.	Y	N	Highly unlikely	Highly unlikely	Risk Zone II (ALARP)
			Sequencer timeline is not correct.		Sequencer cannot process assay.	Delay in reporting patient test results to Physician (or no test results at all)	Permanent Injury						N	N			
14.	Installation of NT and XP from single CD Work Items: 108006, 110020,	Work item specific requirement listed in the work items.	System Software does not install or installs incorrectly	Installation of incorrect files or files in incorrect location	System Software unable to start	Unable to upgrade to newer version. No impact to Patient Safety.	Minor damage	- Inspections at every stage of implementation. - Verification of change.	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable)	- Perform User scenario, Integration test procedure, software installation procedure on both platforms (NT and XP) prior to release.	N	N	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable)
15.	Consolidation of single source code to run on NT and XP platforms Work Item: 107728	Work item specific requirement listed in the work items.	System Software does not operate on the platform it is loaded	Incompatibilities of the System Software across platform	System Software unable to start or shuts down unexpectedly during startup	Unable to run System Software. No impact to Patient Safety.	Minor damage	- Inspections at every stage of implementation. - Verification of change.	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable)	- Perform User scenario, Integration test procedure, software installation procedure on both platforms (NT and XP) prior to release. 09003243 8cc07ca	N	N	Highly unlikely	Highly unlikely	Risk Zone I (Acceptable)

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16.	Help and string updates Work Items: 112837, 112838	No specific requirements, this is the work item used to import the revised help and language files into the build.	Missing links in the help file or missing strings in the user interface.	Broken links to help topics or missing strings in the language files.	User confusion due to the inability to access help topic or unable to navigate the user interface.	User inconvenienced. May require a call to the hotline.	Negligible Injury		Highly Unlikely	Highly Unlikely	Risk Zone I (Acceptable)	- Prescribed verification: Analysis performed in the change point analysis and risk and hazard section of the WIs indicate no additional verification is necessary.	N	N	Highly Unlikely	Highly Unlikely	Risk Zone I (Acceptable)
17.	Message processing performance and lockup correction. Work Items: 142255, 153175, 153176	Work item specific requirement listed in the work items.	System software locks up when receiving Temperature messages. System no longer able to report results.	Message handling does not keep track of message already processed and keeps processing the same message.	System console could lockup and cause delayed results	System becomes locked and is unable report patient test results, Delayed patient test results	Permanent Injury	-Implemented software correction to eliminate root cause of the issue - Inspections at every stage of implementation. - Verification of change.	Occasional	Highly unlikely	Risk Zone II (ALARP)	- Prescribed verification: . Re-execute Temperature Monitoring and Assigned Temperature Detection protocol to verify the integrity of the temperature monitoring implementation has not been compromised by the change.	N	N	Highly Unlikely	Highly Unlikely	Risk Zone I (Acceptable)

2.6.2. Issues identified in currently fielded software

The following Work Items were identified during testing of the System Software version 3.3 and were assessed for impact on safety using PLRAs as referenced.

Work Item Number	Title	EDMS Document	Decision
96487	Database is inconsistent after deleting a calibrator lot.	Access 2 3.3 PLRA WI 96487	No safety or efficacy risk. No actions are required.
133838	No substrate lot number or substrate serial number written to Diagnostics Copy to Disk files	Access 2 3.3 PLRA WI 133838	No safety impact. No actions are required
133840	Diagnostics Copy to Disk Column Header names don't line up with Data in the "Sample_And_Test" section in some foreign languages	Access 2 3.3 PLRA WI 133840	No safety impact. No actions are required
134632	Dialog Box Titles in Extremely Small Font in Japanese and Chinese	Access 2 3.3 PLRA WI 134632	No safety impact. No actions are required
134656	Access 2 NT: Language displayed in Windows wallpaper is incorrect after switching to or from one of the Asian Languages	Access 2 3.3 PLRA WI 134656	No safety impact. No actions are required

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169583	Access 2 XP e system software upgrade scenario issue for Asian Language	Access 2 3.3 PLRA WI 169583	No safety impact. No actions are required

2.6.3. Issues introduced during this release cycle

The Work Items in the table below were identified during testing of the System Software and were subject to a SFMEA.

The following Work Items were identified during testing of the System Software and were found to have no failure mode.

- WI 164712 - Not all temperature points are stored when an Assay is started while the Utility Assay is in progress (see Access 2 3.3 PLRA - Temp Point Collection)

The purpose of this Safety Failure Modes Effects & Analysis (SFMEA) is to document safety-related failure modes and the risk profile for the Access 2 software version 3.3 that will be released with the following software anomalies:

Work Items identified and fixed are included in the table in §2.6.1

ID	Item Name/ Function / Process Step	Software Requirements	Failure Mode (Cause of Hazard)	Failure Cause	System Effect (Hazard)	End Effect (Hazardous Situation)	Severity of Harm (S)	Existing In Place Controls	Pre-Mitigation			Mitigation (Risk Control Measures)	Post-Mitigation		
									OCC	P1	Risk		OCC	P1	Risk
18.	WI 151646-Access 2 Dual Disk: When switching to or from Japanese or Chinese, the system needs to do an automatic reboot when running under NT	NexStep Diagnostics Requirements: REQ45 The console data shall include the combined sample and test results, the rack data, the pack and lot data, and curve data	System is not rebooted after changing language to Japanese or Chinese causing some reports and diagnostic function to fail.	Code to reboot under NT was not merged to the 3.3 version	User has to manually reboot in order to complete the language change.	Nuisance to operator.	Negligible Injury	Information Update document A913628 (Software Installation IU) contains the reboot instructions when switching to or from either Asian language.	Highly unlikely	Highly unlikely	Zone I – Acceptable: Risks that fall in this zone are low and do not require further risk control.	None	N/A	N/A	N/A

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ID	Item Name/ Function / Process Step	Software Requirements	Failure Mode (Cause of Hazard)	Failure Cause	System Effect (Hazard)	End Effect (Hazardous Situation)	Severity of Harm (S)	Existing In Place Controls	Pre-Mitigation			Mitigation (Risk Control Measures)	Post-Mitigation		
									OCC	P1	Risk		OCC	P1	Risk
19.	WI 167525 - QC Copy to Disk does not write to the expected location on the C: drive	NexStep Quality Control Review Requirements: REQ49 The user can save QC data to Windows accessible drives (excluding optical drives). The list of Windows accessible drives shall be generated dynamically.	Software defect causes QC Copy to Disk function to write file to unexpected location.	Software defect	Operator may not be able to locate QC file without assistance.	There is no known workflow requiring the user to attempt to store the QC results to the C: drive.	N/A	Per Operator's guide 105330J section 7.2 user should not attempt to save to the C: drive. Capability by design provides work-around: QC Results Copy to Disk to the floppy disk or Diagnostics Copy to Disk to either C: drive or floppy disk.	N/A	N/A	N/A	None required	N/A	N/A	N/A
20.	WI 167526 - Test Results Copy to Disk to the C: drive does not work for Access 2 running on Windows NT	NexStep Test Results Requirements: REQ50 The user can send the entire list of results to Windows accessible drives (excluding optical drives). The list of Windows accessible drives shall be generated dynamically.	Operator cannot copy test results to the C: drive.	Software defect does not allow Test Results Copy to Disk for Windows NT systems.	Access 2 users who still have a console running Windows NT will be unable to copy test results to the C: drive. An error dialog will be displayed if the user attempts this. Windows XP systems will not have this issue	There is no known workflow requiring the user to attempt to store the Test results to the C: drive.	N/A	Per Operator's guide 105330J section 7.2 user should not attempt to save to the C: drive. Capability by design provides work-around: Test Results Copy to Disk to the floppy disk or Diagnostics Copy to Disk to either C: drive or floppy disk.	N/A	N/A	N/A	None required	N/A	N/A	N/A

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ID	Item Name/ Function / Process Step	Software Requirements	Failure Mode (Cause of Hazard)	Failure Cause	System Effect (Hazard)	End Effect (Hazardous Situation)	Severity of Harm (S)	Existing In Place Controls	Pre-Mitigation			Mitigation (Risk Control Measures)	Post-Mitigation		
									OCC	P1	Risk		OCC	P1	Risk
21.	WI 175688 - Installer always installs some Japanese components even when not requesting Japanese Install (Windows NT only)	Correct the Anomaly	The Installer unconditionally installs Japanese components.	The Installer does not check if the user is installing the Japanese language	Japanese components are installed on the system, Installation may take longer.	No impact as the components installed are not being used, they only take some additional space on the PC hard drive.	N/A	None, the system does not use the components even though they are available.	N/A	N/A	N/A	None required	N/A	N/A	N/A
22.	WI 142574 - Thermally-corrected results flagged CCR after APF update	Correct the Anomaly	Following an APF update, User runs patient samples before restarting the console	Software defect causes thermally-corrected results (TnI only) to be flagged CCR (Fatal) after APF update to the XML file for a thermally corrected assay if user fails to restart console	Results will be suppressed on thermally corrected assays (TnI only)	Delay in patient test results to the Physician on thermally corrected assays (TnI only)	Permanent Injury	Access 2 APF Installation CD Booklet (B14180A) states" "Run quality controls for each assay you will be running with the newly installed APF. If the results are out of range, recalibrate the assay." This activity will expose the problem and drive the hazard elimination (restarting the console) before experiencing a hazardous situation	Remote	Remote	Zone II (As Low As Reasonably Practicable)	New APF instructions instruct user to reboot console after APF load	Remote	Remote	Zone II (As Low As Reasonably Practicable)

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2.7. Risk Control Measures results

All prescribed mitigation test results are captured in the appropriate location for the test. Refer to Team Foundation for the individual work item tests, the Software Testing and Software Validation Summary contains the references to locate objective evidence of successful completion of the other prescribed tests.

Message processing performance and lockup issue (from line 17 above), was corrected and the root cause was eliminated. The corrected software build was tested and verified using the mitigations described above in line 17 to ensure proper functional operation of the system software. Additionally, the design documentation will be updated to capture this failure mode and to ensure that future software designers are aware. See Team Foundation Work Item 153325.

2.8. Acceptability Rationale

Based on the information captured in the Hazard Analysis and the scope statement in the Resolution tab of TFS for each Work Item resulting in software design change, analysis concludes:

- The WI test cases are adequate to verify that the changes are implemented as intended.
- Functionality is sufficiently covered by the test cases listed in the Work Item.
- Design and code reviews determined that any risk identified is effectively mitigated and there is no identified residual risk.

The prescribed testing selected comprehensively verifies/validates all the areas that have been affected by the change.

The planned User Scenario testing will further validate that no new hazards have been introduced in the affected area for each Identified function or Process step and that no other areas are indirectly adversely affected.

Contract developers and contract manufacturers' notification process will be initiated due to the following changes:

- Temperature restrictions (suppress results when case temperature is outside range of 18 to 36°C)
- New file format for Diagnostic Copy To Disk to include temperature related data.
- New ability to load assay specific temperature correction algorithms through the APF.

Specific testing will be performed to ensure that mitigations for the identified risks are effective:

- Systems Integration Assay testing of TnI due to
  - Implementation of algorithm for temperature correction.
  - TnI new pipetting Cycle U

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- The need to confirm that system functionality has not been negatively impacted by the cumulative set of software changes.

- Software verification for non-thermally adjusted assays due to:
  - Suppression of results when case temperature is outside range of 18 to 36°C.
  - Decision to thermally correct an assay.

2.9. Risk Assessment Conclusion

Based on the above risk assessment and description of test coverage, the software verification and software validation testing combined with Systems Integration Assay Testing of TnI is sufficient to ensure the risks associated with the changes in this software version are appropriately mitigated.

Contract developers and contract manufacturers' notification process will be initiated.

For risks that are in Risk Zone II (ALARP) all appropriate testing has been performed and controls put in place whereby the change team considers these risks are as low as reasonably practicable Risk control measures to maintain risks in Risk Zone II (ALARP) represent the generally accepted state of the art where all performance characteristics related to safety meet medical requirements for the intended uses of the instrument and are comparable to other instruments in commercial distribution.

The residual risk for this release is found to be acceptable.

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Appendix A

Document custom properties. **Do not directly edit.**

Project field	Access 2
Revision Field	3.3

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IC 1 – HHE and Risk Assessment Review Record

(Attach to parent document)

Document Type (check one):

☐ Health Hazard Evaluation

HHE Number and Date: _____

☒ Risk Assessment

Risk Assessment Revision and Date: Ver. 1.20 March 20, 2012

Document Name: Access 2 3.3 System Software Change Risk Assessment

Reviewer Name (printed): Mark A. Magnuson

Reviewer Signature: [signature]

Review Date: March 20, 2012

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Appendix 4

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Appendix 4: Access 2 System Risk Assessment (SRA)

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BECKMAN COULTER	Access 2 SRA	Company Template: BCCT0116

ACCESS 2 SRA

<PROJECT NAME>

ACCESS 2 3.3 SOFTWARE (NT/XP)

<PROJECT NUMBER>

CAPA 16241

<DOCUMENT NUMBER>

<REVISION>

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Access 2 SRA	Company Template: BCCT0116

1. Purpose

The purpose of this SRA is to summarize potential failure modes related to safety and corresponding hazardous situations, potential harms, mitigations/risk control measures, and the resulting residual risk profile and its acceptability for the Access 2 3.3 Software Design Change for thermal mitigation. Existing FMEAs are the source documents for this SRA which is limited to the Access 2 Immunoassay instrument and the Access 2 portion of the DxC integrated configurations.

2. Scope

2.1 Product(s) and/or System

The scope of this analysis applies to Access 2 instruments and its system interface with the operators and the environment.

2.2 Intended use

The Access 2 system is an in vitro diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Definitions

Access 2	Access 2, DxC 600i
EDMS	Enterprise Document Management System
PSR	Product Safety Reference

4. Reference Documents

EDMS Object Name	Description
BCCR0001	Lexicon
BCCP0082	Product Safety Risk Management, Corporate Procedure
BCCP0083	Risk Acceptability, Corporate Procedure
BCCP0109	Risk analysis Methods, Corporate Procedure
BCCG0059	Software Risk Management, Corporate Guideline
Thermal Control Algorithm Risk Management Plan	AccuTnI Thermal Risk Management Plan
Access 2 3.3 System Software Change Risk Assessment	Safety FMEA for Software Change
AccuTnI PSR	AccuTnI's Product Safety Reference
Rubella IgM Product Safety Reference	Rubella IgM 's Product Safety Reference
Toxo IgM II Product Safety Reference	Toxo IgM 's Product Safety Reference

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5. Input Documents to the SRA

- *EDMS Object Name : "Access 2 3.3 System Software Change Risk Assessment".*
- Tabulated below are the rows extracted from the PSRs corresponding to assays with Severity (S)/ Probability of Harm (P2) combinations resulting in the highest risk per BCCP0083 risk matrix. These combinations of Severity and P2 are used to score the failure modes in this SRA.
- Note if the hazardous situation is stated as "physician receives incorrect results", the highest-risk Severity/P2 combination is Life Threatening Injury (LTI)/Frequent (F) based on the Rubella IgM PSR.

ID	Product Safety Reference	Hazardous Situation	Severity of Harm (S)	Harm	Probability of Harm (P2)
1	Rubella IgM Product Safety Reference (Version 1.0)	False Positive (High) Result	Life Threatening Injury	The impact is potential injury to the fetus. Patient may receive unnecessary additional testing, including some invasive testing. Depending on the magnitude of the error, the physician may overestimate protection to Rubella. Physician may falsely attribute sera conversion. Physician may falsely diagnose as Rubella like illness due to a reactive recent infection. If infection occurs during pregnancy, patient may not receive appropriate monitoring and/or treatment. Congenital Rubella Syndrome develops in 90% of pregnancies at 8 to 10 weeks, and 20% of pregnancies at 16 weeks. Up to 20% develop Type I Diabetes in 5 -20 years. Spontaneous abortion occurs in up to 20% of cases. Not vaccinating women who are in fact, susceptible to infection.	Frequent
2	Toxo IgM Product Safety Reference (Version 1.0)	False Negative (Low) Result	Life Threatening Injury	Transmission of infection through transfusion or through infected organ. Potential to cause life-threatening disease in previously un-infected individuals.	Occasional
3	AccuTnI PSR (Version 3.4)	Delayed Result	Permanent Injury	Progression of cardiac disease/injury	Highly Unlikely

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6. List of Participants Performing Risk Assessment

Functional area	Name	Participant	Approver
Program Management	Ursula Peterson	X	X
Supply Chain	Scott Matzke	X	X
Quality Assurance	Gordon Frandsen	X	X
Regulatory Affairs	Lynn Weist	X	X
Software Research & Development	François Auradon	X	X
EHS/PCE	Jeff Gonzalez		X
Business Quality Head	Scott Cundy		X

7. Risk Control Options Analysis

All mitigations are design or protective measures.

8. Conclusion

- All individual residual risks are in either Risk Zone 1 (Acceptable) or Risk Zone 2 (ALARP).
- For risks that are in Risk Zone II (ALARP), risk control measures to maintain risks in the ALARP zone represent the generally accepted state of the art where all performance characteristics related to safety meet (medical) requirements for the intended uses of the instrument and are comparable to other instruments in commercial distribution. All appropriate testing has been performed and controls put in place to ensure that risks are low as reasonably practicable.

9. Appendix

None

10. Content Change Abstract

Revision Level	Date	Author Name	Change Description
1.0	3/16/12	David Hurd	Initial Version.
1.1	3/19/12	David Hurd	Review Comments from Mark Magnuson & other reviewers added.
1.2	3/20/12	David Hurd	Made a few more changes based on review comments including filling in TBD cells.

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Access 2 SRA	Company Template: BCCT0116

1.3	3/21/12	G. Frandsen	Attach IC-1 Form.

11. Content Approvals

My electronic signature confirms my approval of this document.

APPROVALS:	APPROVED ON (MM/DD/YYYY):
Peterson, Ursula I	03/21/2012 07:53:45 (PDT)
Frandsen, Gordon	03/21/2012 08:24:42 (PDT)
Auradon, Francois B	03/21/2012 10:51:32 (PDT)
Matzke, Scott D	03/22/2012 08:39:59 (PDT)
Weist, Lynn S	03/23/2012 14:14:41 (PDT)
Cundy, Scott	03/28/2012 11:19:07 (PDT)

12. System Risk Assessment (SRA)

The following tables define the acronyms used to score the severity and P1/P2/P(tot) columns in the SRA chart.

Legend for Severity	
LTI/CD	Life-threatening Injury /Catastrophic Damage
PI/SD	Permanent Injury /Serious Damage
MRI/MaD	Medically Reversible Injury /Major Damage
TI/MiD	Temporary Injury /Minor Damage
NI/ND	Negligible Injury /Negligible Damage

Legend for P1/P2/Ptot	
HL	Highly Likely
F	Frequent
O	Occasional
R	Remote
HU	Highly Unlikely

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access 2 SRA	Company Template: BCCT0116

SRA Risk ID	Source ID	Hazard	Cause of the Hazard	Hazardous Situation	Harm	S	Pre-Mitigation				Method of Control	Risk Control Measure	Verification, Validation Traceability		Post-Mitigation					Notes
							P_1	P_2	P_{total}	Risk Zone			Design Input Spec ID	Test Report	P_1	P_2	P_{total}	Risk Zone	Acceptable Risk?	
1	A2 System SW SFMEA 1	Thermally stimulated result does is intermittently calibrated based on erroneous temperature input data.	Simultaneous temperature values are not accurate.	Physical reactions incorrect SFMEA test results	Harm ID 1, See Section 5 Harm Table	LTI	R	F	R	III	Design	- Prescribed modifications Perform Temperature Monitoring and Assigned Temperature Simulation protocol to verify the integrity of the temperature monitoring implementation.	Requirements are found in Thermal Software Requirements document. REQ 1, REQ 1.1, REQ 1.1.1, REQ 1.1.2, REQ 1.1.3, REQ 2, REQ 3, REQ 4, REQ 4.1	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	
2	A2 System SW SFMEA 1	Unable to calculate adjusted data for Thermally stimulated temp.	Temperature monitoring is not available	Physical reactions incorrect SFMEA test results	Harm ID 1, See Section 5 Harm Table	LTI	HU	F	HU	II	Design	- Prescribed modifications Perform Temperature Monitoring and Assigned Temperature Simulation protocol to verify the integrity of the temperature monitoring implementation.		EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	
3	A2 System SW SFMEA 4	Thermally stimulated result does is intermittently calibrated based on erroneous temperature assignment.	Temperature calibration is incorrect	Physical reactions incorrect SFMEA test results	Harm ID 1, See Section 5 Harm Table	LTI	HU	F	HU	II	Design	- Prescribed modifications Perform Temperature Monitoring and Assigned Temperature Simulation protocol to verify the integrity of the temperature monitoring implementation.	Requirements are found in Thermal Software Requirements document. REQ4, REQ5, REQ6, REQ6.1, REQ6.3.1, REQ6.3.2, REQ6.3.3.	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access 2 SRA — Company Template: **BCCT0116**

4	A2 System SW SFMEA 5	System unable to access Thermal data	Incorrect data stored in the Database	System unable to calculate or report patient test results, Delay in reporting patient test results to Physician	Harm ID 3, See Section 5 Harm Table	PI	HU	HU	HU	II	Design	- Prescribed verification: Perform Data Storage protocol to verify the integrity of the Thermal data retention implementation.	Requirements listed in Thermal Software Requirements document. REQ3, REQ9, REQ9.1, REQ9.2, REQ9.3, REQ9.4, REQ9.5, REQ9.6, REQ9.7	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	HU	HU	II	Yes	
5	A2 System SW SFMEA 6	Incorrect patient test results generated	No correction or incorrect adjusted dose.	Physician receives incorrect patient test results	Harm ID 1, See Section 5 Harm Table	LTI	HU	F	HU	II	Design	- Prescribed verification: Perform Test Result Reporting protocol to verify the integrity of the temperature monitoring implementation.	Requirements listed in Thermal Software Requirements document. REQ4, REQ4.1, REQ5, REQ5.1, REQ6, REQ6.2, REQ6.1, REQ6.1.1, REQ6.1.2, REQ6.1.3, REQ14, REQ14.1, REQ14.2	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	
6	A2 System SW SFMEA 7	Incorrect patient test results generated	APF data improperly managed in the System	Physician receives incorrect patient test results	Harm ID 1, See Section 5 Harm Table	LTI	HU	F	HU	II	Design	- Prescribed verification: Perform Test Result Reporting protocol to verify the integrity of the temperature monitoring implementation.	Requirements listed in Thermal Software Requirements document. REQ5, REQ10, REQ15, REQ15.1	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	

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7	A2 System SW SFMEA 8	[illegible]	[illegible]	[illegible]	[illegible]	PI	HU	HU	HU	II	Design	• Analysis performed in the change point analysis and risk and hazard section of the tab indicate no additional verification other than the test case specified in the test tab of the work item is necessary.	[illegible]	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	HU	HU	II	Yes	
8	A2 System SW SFMEA 9	Thermal correction is not applied on the configuration sheet there is a check to prevent the instrument from thermally correcting the result multiple times	Samples appear as "Replicated" in the sample manager during after the run has been completed and the instrument is in ready mode.	Incorrect patient test results reported in the Physician if a thermal correction is required, however, the correct test result will be reported if no thermal correction is required.	Hazard ID 1, See Section 5 Hazard Table	LTI	HU	F	HU	II	Design	• Analysis performed in the change point analysis and risk and hazard section of the tab indicate no additional verification other than the test case specified in the test tab of the work item is necessary.	Requirements not listed in Section Data Reduction Requirements as RC07 Detailed Work Item Requirements Result cause is not to TI_COMP, ITCD after the result has been successfully calculated.	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	
9	A2 System SW SFMEA 12	System software testing of new algorithm may produce erroneous patient test results generated.	Changes to the algorithm following system software verification.	Physician receives inaccurate patient test results	Hazard ID 1, See Section 5 Hazard Table	LTI	O	F	O	III	Design	• Prescribed verifications by-necessary test cases related to result and algorithm either standalone test case TI1 or test cases embedded in an implementation WI.	Requirements not listed in Thermal Software Requirements as documents.	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	
10	A2 System SW SFMEA 13	Incorrect patient test results generated	Mixing not performed correctly.	Physician receives incorrect patient test results	Hazard ID 1, See Section 5 Hazard Table	LTI	O	F	O	III	Design	• Perform appropriate verification and validation of the new UI centrifuge prior to implementation for release. Software validation	Work Item specific requirements as listed in the work items.	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	II	Yes	

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Access 2 SRA — Company Template: **BCCT0116**

11	A2 System SW SFMEA 13	[illegible]	[illegible]	[illegible]	[illegible]	Pi	O	HU	HU	II	Design	[illegible]	[illegible]	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	HU	HU	2	Yes	
12	A2 System SW SFMEA 14	[illegible]	[illegible]	[illegible]	[illegible]	MD	HU	F	HU	I	Design	[illegible]	[illegible]	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	I	Yes	
13	A2 System SW SFMEA 15	[illegible]	[illegible]	[illegible]	[illegible]	MD	HU	F	HU	I	Design	[illegible]	[illegible]	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	I	Yes	
14	A2 System SW SFMEA 16	[illegible]	[illegible]	[illegible]	[illegible]	MI	HU	F	HU	I	Design	[illegible]	[illegible]	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	HU	F	HU	I	Yes	

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Access 2 SRA

Company Template: BCCT0118

15	A2 System SW SFMEA 17	System remote could hang and show delayed results	System software fails up when supplying Temperature messages. System no longer able to report results. Delayed patient test results	System becomes hung and is unable report patient test results. Delayed patient test results	Mem ID 3, See Section 5 Mem Table	PI	O	HU	HU	II	Design	• Prescribed notifications • Re-initiate Temperature Monitoring test • Assigned Temperature Indication prepared to verify the integrity of the temperature monitoring implementation has not been compromised by the change	Work Area specific requirement as listed in the work items.	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	N/A	N/A	N/A	Failure Mode Eliminated	Yes	
16	A2 System SW SFMEA 18	User has to manually reboot in order to complete the language change.	System is not rebooted after changing language to Japanese or Chinese showing wrong reports and diagnostic function to fail.	Inadequate to operator.	Insignificant Delay in Management Operations	MI	HU	HL	HU	I	N/A	None required.	Handling Complaints Requirements refer SOP#5 The remote data shall include the combined sample and test results, the start date, the work and list date, and error data	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	N/A	N/A	N/A	I	Yes	
19	A2 System SW SFMEA 22	Results will be suppressed on chemically contaminated sample (Test only)	Following an ARF update, User runs patient samples before restarting the remote	Delay in patient test results to the Physician on chemically contaminated sample (Test only)	Mem ID 3, See Section 5 Mem Table	PI	R	HU	HU	II	Instructions	New ARF instructions correct error to reboot remote after ARF load	Correct the Instructions	EDMS Doc: Access 2 3.3 Software Testing & Software Validation Summary	R	HU	HU	II	Yes	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access 2 SRA

IC 1 – HHE and Risk Assessment Review Record

(Attach to parent document)

Document Type (check one):

☐ Health Hazard Evaluation

IIHE Number and Date: _____

☒ Risk Assessment

Risk Assessment Revision and Date: Ver. 1.3 March 20, 2012

Document Name: Access 2 SRA

Reviewer Name (printed): Mark A. Magnuson

Reviewer Signature: _____

Review Date: March 20, 2012

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 5

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 5: Thermal Software Requirements

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 31

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 31: Labeling

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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See redlistch

Access Reagents:

BECKMAN COULTER

Access
Access AccuTnI

REAGENT
REF A98143

IVD 用于体外诊断

肌钙蛋白I測定试剂盒 (化学发光法)

For use on Access 2 platforms only.
Para uso exclusivo en sistemas Access 2.
Yalnız Access 2 platformlarında kullanılmak içindir.
Для использования только с платформами Access 2.
Access 2 用

10°C
2°C

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Printed in U.S.A.

B00538C

BECKMAN COULTER

Access ベックマン・コールター株式会社
Access AccuTnI

REAGENT
REF A98143

Access REAGENT II
Access AccuTnI

LOT

2 x 50 Tests/回用

R1a: 3.25 mL	Paramagnetic particles coated with mouse monoclonal anti-human cTnI, TRIS, surfactant, BSA.	固相試薬：磁性粒子結合抗ヒトトロポニン I マウスモノクローナル抗体
R1b: 9.95 mL	0.1 N NaOH	プローブ洗浄液：水酸化ナトリウム
R1c: 3.10 mL	TRIS buffered saline with surfactant.	緩衝液：トリス緩衝液
R1d: 3.10 mL	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, ACES, surfactant, protein (bovine, goat, mouse).	コンジュゲート試薬：アルカリホスファターゼ結合抗ヒトトロポニン I マウスモノクローナル抗体

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体外診断用医薬品

B00539A

CE

Access
Access AccuTnI

REAGENT
REF A98143

2 reagent packs R1, for the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.

2 envases de reactivos R1, para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.

Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini niceliksel olarak tespit etmek için 2 reaktif paketi R1.

2 комплекта реагентов R1 для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.

クラスIII生化学・免疫：内分泌検査用シリーズ　トロポニンキット　/　アクセス AccuTnI 試薬/パック

Xi, ≥ 0.0375 – < 1.5% ProClin™ 300
R 43, S 28-37

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B00540B

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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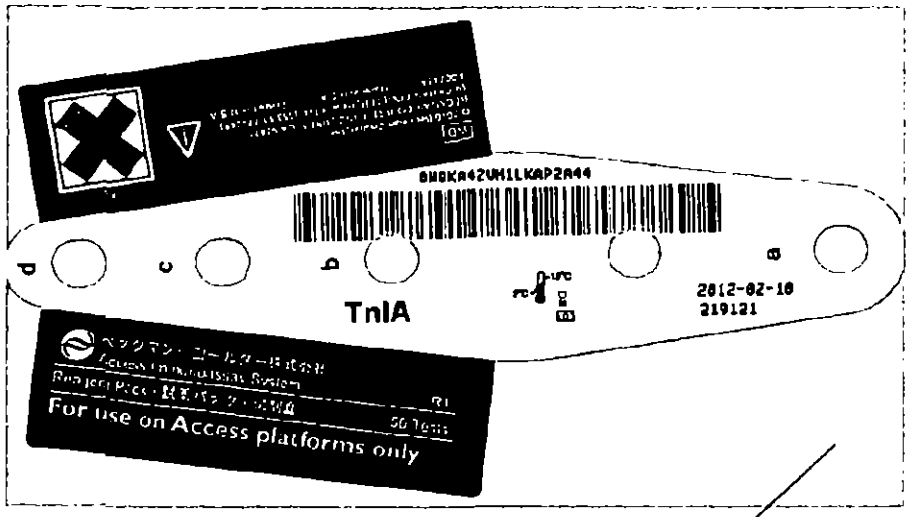

Accu-Lot the Access 2 Immunoassay System
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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See reverse

Access Calibrators:

BECKMAN COULTER

Access

CALIBRATORS S0 S1 S2

Access AccuTnI CALIBRATORS REF **A98144**

IVD 用于体外诊断

肌钙蛋白I 测定试剂盒 (化学发光法)

For use on Access 2 platforms only.
Para uso exclusivo en sistemas Access 2.
Yalnız Access 2 platformlarında kullanılmak içindir.
Для использования только с платформами Access 2.
Access 2 用

*2–10°C after opening / après ouverture / después de abrir / dopo l'apertura / nach dem Öffnen / após a abertura / efter öppning / efter åbning / po otwarciu / Açıldıktan sonra / после вскрытия / Aldarfus lokyd / 開封後は保存 / 开封后储存 / efter at den er åbnet / съхранение на след отваряне

-20°C

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B00535C

BECKMAN COULTER

Access

CALIBRATORS S0 S1 S2

Access AccuTnI CALIBRATORS REF **A98144**

1 x 1.5 mL	S0	BSA matrix, surfactant.	ウシ血清アルブミン
1 x 1.5 mL	S1	BSA matrix, surfactant, recombinant cTnI.	リコンビナント心筋由来トロポニン複合体，ウシ血清アルブミン
4 x 1.0 mL	S2–S5	BSA matrix, surfactant, recombinant cTnI.	リコンビナント心筋由来トロポニン複合体，ウシ血清アルブミン

1 Calibration Card/Carte d'étalonnage/Tarjeta de calibración/Scheda di taratura/Kalibratorkarte/Cartão de calibração/Kalibreringskort/Karcie kalibracji/Kalibrasyon kartı/Калибровочная карта/Kalibraimo korteleje/キャリブレーションカード / 定标卡。/Калибрационна карта

S0: 0 ng/mL 0 µg/L | S1: ~0.3 ng/mL ~0.3 µg/L | S2: ~1.2 ng/mL ~1.2 µg/L | S3: ~5.0 ng/mL ~5.0 µg/L | S4: ~25 ng/mL ~25 µg/L | S5: ~100 ng/mL ~100 µg/L

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B00536B

Access

CALIBRATORS S0 S1 S2 II

Access AccuTnI CALIBRATORS

LOT

CE

Access

CALIBRATORS S0 S1 S2

Access AccuTnI CALIBRATORS REF **A98144**

CALIBRATORS	For the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.
CALIBRADORES	Para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.
KALİBRATÖRLER	Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini niceliksel olarak tespit etmek için.
КАЛИБРАТОРЫ	Для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.
キャリブレータ	トロポニンキット用 / アクセス AccuTnI キャリブレータ

Xi. ≥ 0.0375 – < 1.5% ProClin™ 300
R 43, S 28-37

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For use on Access platforms only

S0

Access AccuTnI

1.5 mL

Calibrator • キャリブレータ • CAL

IVD

Made in U.S.A. Printed in U.S.A.
BECKMAN COULTER, INC., Brea, CA 92821
BECKMAN COULTER, Ireland Tel. (353 91 774068)

-20°C*
* 2 to 10°C after opening

0 ng/mL

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Xi.

B00541B

For use on Access platforms only

S1

Access AccuTnI

1.5 mL

Calibrator • キャリブレータ • CAL

IVD

Made in U.S.A. Printed in U.S.A.
BECKMAN COULTER, INC., Brea, CA 92821
BECKMAN COULTER, Ireland Tel. (353 91 774068)

-20°C*
* 2 to 10°C after opening

~0.3 ng/mL

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B00542B

For use on Access platforms only

S2

Access AccuTnI

1.0 mL

Calibrator • キャリブレータ • CAL

IVD

Made in U.S.A. Printed in U.S.A.
BECKMAN COULTER, INC., Brea, CA 92821
BECKMAN COULTER, Ireland Tel. (353 91 774068)

-20°C*
* 2 to 10°C after opening

~1.2 ng/mL

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B00543A

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S3

Access AccuTnI

1.0 mL

Calibrator • キャリブレータ • CAL

IVD

Made in U.S.A. Printed in U.S.A.
BECKMAN COULTER, INC., Brea, CA 92821
BECKMAN COULTER, Ireland Tel. (353 91 774068)

-20°C*
* 2 to 10°C after opening

~5.0 ng/mL

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B00544A

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For use on Access platforms only

S4

Access AccuTnI

1.0 mL

Calibrator • キャリブ[illegible] CAL

IVD

S4

Made in U.S.A. Print[illegible] in U.S.A.
BECKMAN COULTE[illegible] INC. [illegible]a, CA 928[illegible]
BECKMAN COULTER, [illegible] Tel. (353 9[illegible]74068)

-20°C*
* 2 to 10°C after opening
~25 ng/mL

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Xi.

B00545A

For use on Access platforms only

S5

Access AccuTnI

1.0 mL

Calibrator • キャリブ[illegible] CAL

IVD

S5

Made in U.S.A. Print[illegible] in U.S.A.
BECKMAN COULTE[illegible] INC. [illegible]a, CA 928[illegible]
BECKMAN COULTER, [illegible] Tel. (35[illegible]74068)

-20°C*
* 2 to 10°C after opening
~100 ng/mL

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B00546A

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Access REF A98144
CALIBRATION CARD

LOT 219288 2012-02-14

AccuTnI for use on Access

14721928814FEB12

S0 LOT 219288 147S00

S1 LOT 219288 147S10.298

S2 LOT 219288 147S21.168

S3 LOT 219288 147S35.14

S4 LOT 219288 147S425.3

S5 LOT 219288 147S596

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See NUSEL

Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI

REF A98143 FOR USE ON ACCESS SYSTEMS WITH TEST NAME: TnIA

Intended Use

The Access AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In acute myocardial infarction (AMI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post AMI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a myocardial infarction (MI), which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11]

Definition of Acute Myocardial Infarction

In 2007, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology (ACC), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[11] Professional groups are now united in establishing cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The published 2007 universal definition of MI states that the following is one criteria for the diagnosis of MI:

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- "Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia;
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality."[11]

Additionally, the universal MI definition consensus document recommends an imprecision level (coefficient of variation, or CV) for troponin assays less than or equal to 10% at the 99th percentile URL of a healthy population.[11]

When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[12] Serial measurements of cTn are necessary when cTn is not elevated upon admission as cTn may not appear in blood within the first hours after myocardial injury.[13] As such, cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise or fall in cTn levels.

Principles of the Procedure

The Access AccuTnI assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI Reagent Pack (for use on Access systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[14]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
107	0.01–20	0.00 (0.00–0.00)	1.00 (0.98–1.00)	1.00
104	0.01–5	0.00 (0.00–0.00)	1.00 (1.00–1.00)	1.00

Heparin plasma and serum samples **should not be used interchangeably.**[15]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[16,17,18] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[16]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[16]
   - Keep tubes stoppered at all times.[16]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[16]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.

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3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI Calibrators (for use on Access systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[19] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing.
3. Samples can be accurately measured within the analytical range of the assay (approximately 0.01–100 ng/mL [µg/L]).
   - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value (i.e., < 0.01 ng/mL [µg/L]).
   - If a sample contains more than the stated value of the highest Access AccuTnI Calibrator (S5), report the result as greater than that value (i.e., > 100 ng/mL [µg/L]).
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[20,21] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[22,23] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[24] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[16,17,18] Following blood collection tube manufacturers' specimen collection and handling recommendations will help to reduce preanalytical error.
7. The Access AccuTnI assay is not intended to be used in isolation and medical decisions should not be based on a single AccuTnI determination at one time point.[15] Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[11]
8. The Access AccuTnI assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Clinical Performance Evaluation

As described in the Summary and Explanation section of this document, the universal definition of MI/AMI has promoted the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI to aid in the diagnosis of MI, a clinical study was designed and executed to identify sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

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A multicenter prospective cohort study was performed, enrolling 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). Subjects who met the following criteria were considered eligible for inclusion in the study:

- Provided written informed consent.
- Were ≥ 21 years of age.
- Presented to the ED with chest discomfort or equivalent ischemic symptoms occurring at rest, lasting ≥ 5 minutes and were consistent with myocardial ischemia symptoms.
- Had a 12-lead electrocardiogram (ECG) taken at time of presentation to the ED.
- Had a minimum of 3 blood collections within 24 hours of presentation to the ED, however, subjects with only 2 collections were included if immediate intervention was required per the standard-of-care and a 3rd collection could not be performed without delaying treatment.

In addition to meeting the eligibility criteria, each subject's diagnosis was reviewed by a central adjudication panel consisting of three members with clinical expertise in the diagnosis of MI. Each subject's case report form was reviewed independently by two members of the adjudication panel and they made an independent diagnosis consistent with the Universal Definition of MI.[11] If there was disagreement in the diagnoses from the first two panel members, the third member was asked to make a diagnosis. The panelists were blinded to the attending physician's original diagnosis. Case report forms included information regarding patient history, symptoms, ECG, and troponin values from the facility's standard-of-care device.

A total of 1929 of subjects were evaluated in the testing. Two hundred fifty three (253) were diagnosed with MI, and 217 had at least one elevated troponin with diagnoses other than MI (see table Reasons for Elevated Troponin Values in Non-MI Patients). To assess performance of the Access AccuTnI assay, all samples were tested at one of five independent testing facilities on an Access 2 System. All testing was performed using lithium heparin plasma samples which were collected at baseline and multiple time points following admission: 1–3 hours, 3–6 hours, and 6–9 hours. Data was analyzed at time points following admission and also at time after symptom onset.

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements if < 8 hours after symptom onset; a single negative troponin measured ≥ 8 hours after symptom onset may be used to rule out MI in the ED in the context of the patient's clinical presentation and history.[29] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations.[11,30]

Clinical Sensitivity and Specificity

Clinical sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) were calculated at values near the URL. Sensitivity and specificity results are shown in the tables below for values < 8 hours after symptom onset and ≥ 8 hours after symptom onset and values between 0.02 and 0.10 ng/mL at baseline, and multiple time points following admission 1–3 hours, 3–6 hours, and 6–9 hours. The sensitivity and specificity was calculated from the data from the prospective clinical trial described above and used the adjudicated decision of MI as the clinical endpoint.

Results < 8 Hours After Symptom Onset

TnI cutoff (≥) (ng/mL)	Sensitivity			Specificity		
	%	n/N	95% CI	%	n/N	95% CI
0.02	96.4	159/165	93.5–99.2	83.2	826/993	80.9–85.5
0.03	91.5	151/165	87.3–95.8	89.1	885/993	87.2–91.1
0.04	85.5	141/165	80.1–90.8	93.6	929/993	92.0–95.1
0.05	78.2	129/165	71.9–84.5	95.5	948/993	94.2–96.8
0.06	72.7	120/165	65.9–79.5	96.9	962/993	95.8–98.0
0.10	53.9	89/165	46.3–61.5	98.3	976/993	97.5–99.1

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Results ≥ 8 Hours After Symptom Onset

TnI cutoff (≥) (ng/mL)	Sensitivity			Specificity		
	%	n/N	95% CI	%	n/N	95% CI
0.02	96.9	154/159	94.1–99.6	81.7	909/1113	79.4–83.9
0.03	94.3	150/159	90.7–97.9	86.8	966/1113	84.8–88.8
0.04	88.1	140/159	83.0–93.1	92.7	1032/1113	91.2–94.2
0.05	79.2	126/159	72.9–85.5	94.9	1056/1113	93.6–96.2
0.06	73.0	116/159	66.1–79.9	96.3	1072/1113	95.2–97.4
0.10	60.4	96/159	52.8–68.0	98.7	1099/1113	98.1–99.4

Results at Baseline Measurement (Admission to ED)

TnI cutoff (≥) (ng/mL)	Sensitivity			Specificity		
	%	n/N	95% CI	%	n/N	95% CI
0.02	92.1	233/253	88.8–95.4	84.3	1412/1675	82.6–86.0
0.03	87.4	221/253	83.3–91.4	89.3	1495/1675	87.8–90.7
0.04	77.1	195/253	71.9–82.3	93.9	1572/1675	92.7–95.0
0.05	65.6	166/253	59.8–71.5	95.6	1602/1675	94.7–96.6
0.06	59.7	151/253	53.6–65.7	97.0	1625/1675	96.2–97.8
0.10	44.7	113/253	38.5–50.8	98.6	1651/1675	98.0–99.1

Results at 1–3 Hours Post Admission to the ED

TnI cutoff (≥) (ng/mL)	Sensitivity			Specificity		
	%	n/N	95% CI	%	n/N	95% CI
0.02	98.4	122/124	96.2–100.0	85.5	867/1014	83.3–87.7
0.03	96.0	119/124	92.5–99.4	89.4	907/1014	87.6–91.3
0.04	89.5	111/124	84.1–94.9	93.5	948/1014	92.0–95.0
0.05	80.6	100/124	73.7–87.6	95.8	971/1014	94.5–97.0
0.06	74.2	92/124	66.5–81.9	97.0	984/1014	96.0–98.1
0.10	54.0	67/124	45.3–62.8	98.8	1002/1014	98.2–99.5

Results at 3–6 Hours Post Admission to the ED

TnI cutoff (≥) (ng/mL)	Sensitivity			Specificity		
	%	n/N	95% CI	%	n/N	95% CI
0.02	98.1	154/157	95.9–100.0	81.0	762/941	78.5–83.5
0.03	94.9	149/157	91.5–98.3	86.7	816/941	84.5–88.9
0.04	87.3	137/157	82.0–92.5	93.0	875/941	91.4–94.6
0.05	79.0	124/157	72.6–85.4	95.0	894/941	93.6–96.4
0.06	72.0	113/157	64.9–79.0	96.4	907/941	95.2–97.6
0.10	54.8	86/157	47.0–62.6	98.3	925/941	97.5–99.1

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Results at 6–9 Hours Post Admission to the ED

TnI cutoff (≥) (ng/mL)	Sensitivity			Specificity		
	%	n/N	95% CI	%	n/N	95% CI
0.02	93.0	40/43	85.4–100.0	76.4	188/246	71.1–81.7
0.03	90.7	39/43	82.0–99.4	87.0	214/246	82.8–91.2
0.04	90.7	39/43	82.0–99.4	93.1	229/246	89.9–96.3
0.05	86.0	37/43	75.7–96.4	94.7	233/246	91.9–97.5
0.06	79.1	34/43	66.9–91.2	95.9	236/246	93.5–98.4
0.10	74.4	32/43	61.4–87.5	98.4	242/246	96.8–100.0

Optimal sensitivity and specificity is achieved by using a 0.03 ng/mL clinical decision point. The Access AccuTnI assay demonstrates a total coefficient of variation of 10% at this clinical decision point.

The Access AccuTnI is not intended to be used in isolation and medical decisions should not be based on a single AccuTnI determination at one time point.[15] Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[11]

Non-MI patients with elevated cTnI values (Cardiac Muscle Damage)

Other conditions resulting in myocardial injury can contribute to elevated cTnI levels. These conditions include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non cardiac surgery, extreme exercise, drug-induced damage (cocaine, amphetamine, and others), end stage renal disease, and rhabdomyolysis with cardiac injury. Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a myocardial infarction (MI), which highlights the importance of serial monitoring when the clinical scenario is confusing.[8]

There were 1676 non-MI patients identified in this study. Of these non-MI patients, 217 (13%) had troponin values greater than or equal to 0.03 ng/mL on one or more of the serial collections. The table below lists the diagnoses for the subjects with elevated troponin levels not attributable to MI. Results are consistent with literature findings that troponin may be elevated in coronary and non coronary disease in the presence of myocardial injury.[8,9,10,12]

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Reasons for Elevated Troponin Values in Non-MI Patients	n/217 (%)
Stable angina	11 (5.1)
Unstable angina	20 (9.2)
Atrial fibrillation/flutter	34 (15.7)
COPD or Asthma	28 (12.9)
Cancer	14 (6.5)
Cardiomyopathy	9 (4.1)
Cardiotoxic Drugs	14 (6.5)
Carditis	2 (0.9)
Chronic Kidney Disease or Renal Failure	73 (33.6)
Cirrhosis	2 (0.9)
Coronary Artery Disease (CAD)	108 (49.8)
Deep Vein Thrombosis	5 (2.3)
Diabetes Mellitus	90 (41.5)
Dyslipidemia or Hypercholesterolemia	128 (59.0)
Heart Failure	111 (51.2)
Hypertension (HTN)	179 (82.5)
Infection (e.g. HIV, Hepatitis, Sepsis, etc.)	28 (12.9)
Pacemaker/Defibrillator (ICD)	10 (4.6)
Peripheral Vascular Disease (PVD) or Peripheral Artery Disease (PAD)	19 (8.8)
Prior Acute Myocardial Infarction (AMI)	83 (38.2)
Prior Coronary Artery Bypass Graft (CABG)	43 (19.8)
Prior Coronary Artery Stent or Angioplasty	65 (30.0)
Prior Stroke or Cerebral Vascular Accident	31 (14.3)
Pulmonary Embolism	10 (4.6)
Stroke	5 (2.3)
Tachycardia	12 (5.5)
Other Cardiac Condition	21 (9.7)

Note: Total number of subjects and percentages may not add to 100% because patients may have more than one condition.

Risk Stratification for NSTEMI/UA Patients

In a separate study conducted in 2003 with a previous version of Access AccuTnI,[31] results were analyzed from 1736 patients diagnosed with NSTEMI/UA. Patients were seen in follow-up at 30 days and every three months thereafter. Follow-ups continued for an average of one year (minimum of six months). Over the duration of the study, patients were monitored for adverse cardiac events which included death, MI, and recurrent ischemia at rest, leading to rehospitalization and UR. Blood samples were obtained from all patients and were tested for troponin concentrations by the Access AccuTnI assay.

Results were evaluated at cutoffs of 0.04 ng/mL and 0.06 ng/mL. Cardiac troponin I concentrations can be used to risk stratify NSTEMI/UA patients for both short-term (42 days) and longer-term (10 months) assessment for potential adverse cardiac events (death, MI, UR). Cardiac troponin I levels provide useful prognostic information and aid in the risk stratification of NSTEMI/UA patients. This association was shown to be independent of the following covariates: risk factors for CAD, prior history of CAD, drugs used in two weeks prior to enrollment, drugs used during hospitalization, sex, race, and age. The results from this study indicate that elevated troponin levels are independently and significantly associated with an increased risk of adverse cardiac events in patients diagnosed with NSTEMI/UA.

The Access AccuTnI results should be interpreted in light of total clinical presentation of the patient, including: medical history, physical examination, ECG, and biochemical cardiac marker measurements.

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Apparently Healthy Adults

1. Each laboratory should establish its own reference ranges to assure proper representation of specific populations and sample types, and to reflect current practice and criteria for MI/AMI diagnosis at their institution.
2. In one study, the 99th percentile URL using lithium heparin plasma samples for a specific population of apparently healthy adults with no known cardiac disease was determined. Subjects were selected from seven geographically diverse locations and were required to be ≥ 18 years of age, apparently healthy and able to provide written informed consent. Both male and female subjects were included with approximately half above the age of 40 and the other half between 18 and 40. Subjects were excluded from the study if they met any of the following criteria:
   - Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
   - Currently taking a medication for cardiovascular disease, including: ACE inhibitors, Angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
   - Diabetes.
   - Chronic kidney disease.
   - Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosis, rheumatoid arthritis, and/or scleroderma.
   - Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
   - Pregnancy.

   The observed 99th percentile for this population is shown in the following table:

	n	Age Range	99th Percentile (95% CI)
Total	527	18–94	0.02 ng/mL (0.01–0.05)
Male	212	#	0.02 ng/mL (0.01–0.06)
Female	315	#	0.02 ng/mL (0.01–0.05)

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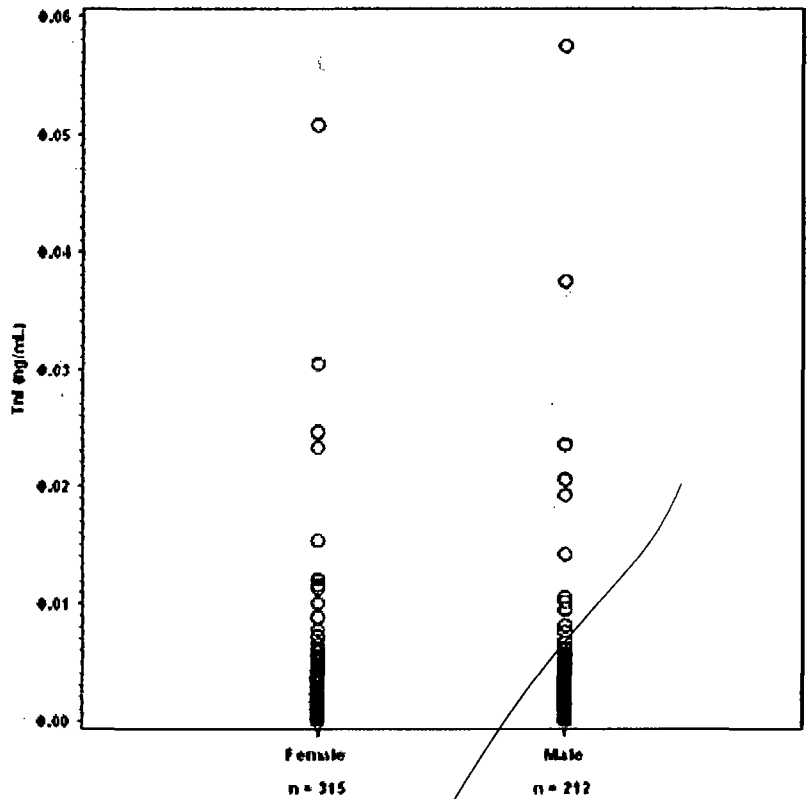
Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

The graph below illustrates the distribution of samples for males and females.



3. Imprecision of Access AccuTnI demonstrates a total coefficient of variation of ≤ 10% at 0.03 ng/mL, which falls within the 95% confidence interval of the 99th percentile URL from the sample population above.

Specific Performance Characteristics

Methods Comparison

A comparison of 1717 lithium heparin plasma values using the Access AccuTnI assay on the Access 2 system and a commercially available immunoassay system gave the following statistical data:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
1717	0.01–50	0.00 (0.00–0.00)	0.68 (0.67–0.69)	0.98
1664	0.01–5	0.00 (0.00–0.00)	0.70 (0.70–0.71)	0.98

Linearity

Twelve studies, based on CLSI EP6-A,[25] were performed to determine linearity of the Access AccuTnI assay. For each study, one high sample (≥ 100 ng/mL) and one low sample (≤ 0.01 ng/mL) were mixed to make nine evenly distributed sample concentrations plus two additional low concentrations. Four replicates of the nine mixed samples, eight replicates of the low sample and two replicates of the high sample were run on an Access 2 system. The Access AccuTnI assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of < 16% for samples > 0.105 ng/mL (µg/L), and < 0.0168 ng/mL (µg/L) for samples ≤ 0.105 ng/mL (µg/L).

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations greater than 0.105 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.0084 ng/mL (µg/L) at concentrations ≤ 0.105 ng/mL (µg/L). One study, based on CLSI EP5-A2[26] guidelines, provided the following data. This study used two patient pools and three commercial controls, tested in duplicate in two runs per shift, two shifts per day, over a minimum of 10 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Patient Pool	0.07	5.0	5.0	7.1
Commercial Control 1	0.91	2.0	5.0	5.4
Commercial Control 2	1.96	2.2	4.9	5.3
Commercial Control 3	13.97	2.3	4.7	5.2
High Patient Pool	56.36	5.1	3.9	6.4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at two concentrations of cTnI (0.01 ng/mL and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. All cTnI values obtained in the presence of each substance were less than ± 10% of the control. This study was run on three Access 2 systems and values were calculated as described in CLSI EP7-A2.[27] Data below represents the highest substance concentrations tested.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	48.75 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL
Furosemide	3 mg/dL

Substance	Highest Concentration Added
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	71 µg/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/dL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	200 µg/mL
Sodium Heparin	28.8 U/mL
Theophylline	25 mg/dL
Triglycerides	500 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 system. Values for cross-reactivity were calculated as described in CLSI EP7-A2.[27] No significant (< 1%) cross-reactivity was observed.

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	1000
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A.[28] A total number of 156 replicates of a zero analyte sample (S0 calibrator) were measured in 12 runs using multiple reagent and calibrator lots on three Access 2 systems.

Limit of Detection

The Access AccuTnI assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI to be 0.005 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A.[28] Three replicates from five low-level heparin plasma samples were measured using multiple reagent and calibrator lots in 12 runs on three Access 2 systems.

Limit of Quantitation

Nine studies, based on CLSI EP17-A,[28] were performed to determine the Limit of Quantitation (LoQ) of the Access AccuTnI assay. Each study tested seven samples in triplicate, in two runs per shift, two shifts per day, over a minimum of 10 days using one Access 2 system and one reagent lot. In the nine studies a total of six Access 2 systems, three lots of reagents, and two calibrator lots were used.

To estimate the expected imprecision in the clinically relevant concentration range, data from the nine studies were pooled together. A three-parameter logistic model was fitted to the pooled data. Combining the results from all studies, the Access AccuTnI LoQ was 0.03 ng/mL (µg/L) at 10% CV and 0.01 ng/mL (µg/L) at 20% CV.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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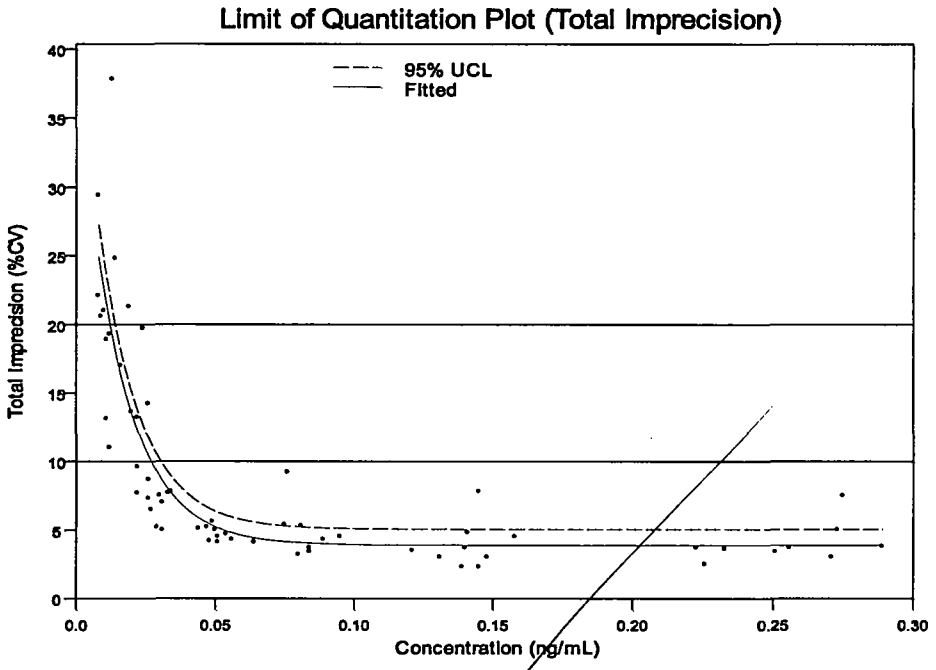

The individual study results are shown in the table below:

Study #	Limit of Quantitation Dose (ng/mL)	
	10% CV	20% CV
1	0.02	< 0.01
2	0.02	0.01
3	0.02	< 0.01
4	0.03	< 0.01
5	0.02	< 0.01
6	0.02	0.01
7	0.04	0.02
8	0.03	0.02
9	0.03	0.01

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI CALIBRATORS

REF A98144 FOR USE ON ACCESS SYSTEMS WITH TEST NAME: TnIA

Intended Use

The Access AccuTnI Calibrators are intended to calibrate the Access AccuTnI assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Cardiac troponin I determination aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI Calibrators (for use on Access systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[14]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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CE

BECKMAN COULTER

Access 2
IMMUNOASSAY SYSTEM

Instructions for Use
for *In Vitro* Diagnostic Use

P/N B14255A - DRAFT
March 12, 2012

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Publication Notes

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All pages of this manual are issued as revision P/N B14255A - DRAFT, release date 3/12/12.

This manual is intended for use with the Access 2 Immunoassay System. This manual also can be used as supplemental material for the UniCel DxC 600i and the SYNCHRON LXi 725 systems, which consist of an Access 2 system integrated with another Beckman Coulter system.

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Table of Contents

1 System Overview 1-1

- Intended Use 1-1
- Scope of Manual 1-1
- Reference Materials 1-1
- Technical Support 1-1
- System Description 1-2
- System Modes 1-3
- System Status Buttons 1-3
- System Command Buttons 1-5
- Main Menu Workflow 1-6
- Precautions and Hazards 1-7
- System Specifications and Characteristics 1-12
- Electrical Requirements 1-13
- Installation 1-16
- Warranty 1-16

2 Shut Down and Restart 2-1

- Rebooting the PC 2-1
- Rebooting the Instrument 2-3
- Shutting Down the Instrument 2-4
- Restarting the Instrument 2-5

3 Supplies 3-1

- Changing the Wash Buffer Bottle 3-1
- Changing the Liquid Waste Bottle 3-2
- Changing the Substrate Bottle 3-3
- Loading Reaction Vessels (RVs) 3-4
- Changing the Reaction Vessel Waste Bag 3-5
- Loading a Reagent Pack 3-6
- Unloading a Reagent Pack 3-7
- Retrieving Misplaced Reagent Packs 3-8

4 Racks and Sample Containers 4-1

- Racks 4-1
- Calculating Sufficient Sample Volume 4-1
- Sample Containers 4-2

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5 Sample Manager 5-1

- Processing LIS Patient Test Requests 5-2
- Entering Patient Test Requests Manually 5-3
- Entering Calibration Test Requests 5-4
- Entering Quality Control Test Requests 5-5
- Processing Samples 5-6

6 Maintenance 6-1

- Daily Maintenance 6-1
- Weekly Maintenance 6-4
- System Check 6-10
- Maintenance Log 6-12

7 Troubleshooting 7-1

- Event Log 7-1
- Troubleshooting Events 7-1
- System Check Troubleshooting 7-3
- Instrument Troubleshooting 7-13
- Assay Troubleshooting 7-20

8 Theory of Operation 8-1

- Reaction Vessel Transport 8-1
- Assay Calibration Theory 8-2
- Obstruction Detection Theory 8-4

A Ordering Information A-1

- Assay-Specific Reagents A-1
- System Supplies A-5

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1 System Overview

Intended Use

The Access 2 system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Scope of Manual

The Access 2 *Instructions for Use* is intended for use after you have become familiar with the Access 2 system. The *Instructions for Use* contains short instructions for everyday use and routine maintenance. It also contains general information about the Access 2 instrument, such as theory of operation, system specifications, safety labeling, and troubleshooting.

NOTE

Regardless of the frequency with which you perform a procedure, regularly review the complete procedures, including their cautions for protecting the instrument from damage, and their warnings for ensuring your personal safety.

Reference Materials

Additional Access 2 system documentation is listed in Appendix A. For more information, contact your Beckman Coulter representative.

Technical Support

For technical assistance with the Access 2 Immunoassay System:

- In the U.S.A. or Canada, contact Beckman Coulter Technical Support by phone at 800-854-3633, or online at www.beckmancoulter.com. Before using online support the first time, you will need to register online.
- Outside the U.S.A. and Canada, contact your technical support representative.

NOTE

Be prepared to provide your system ID.

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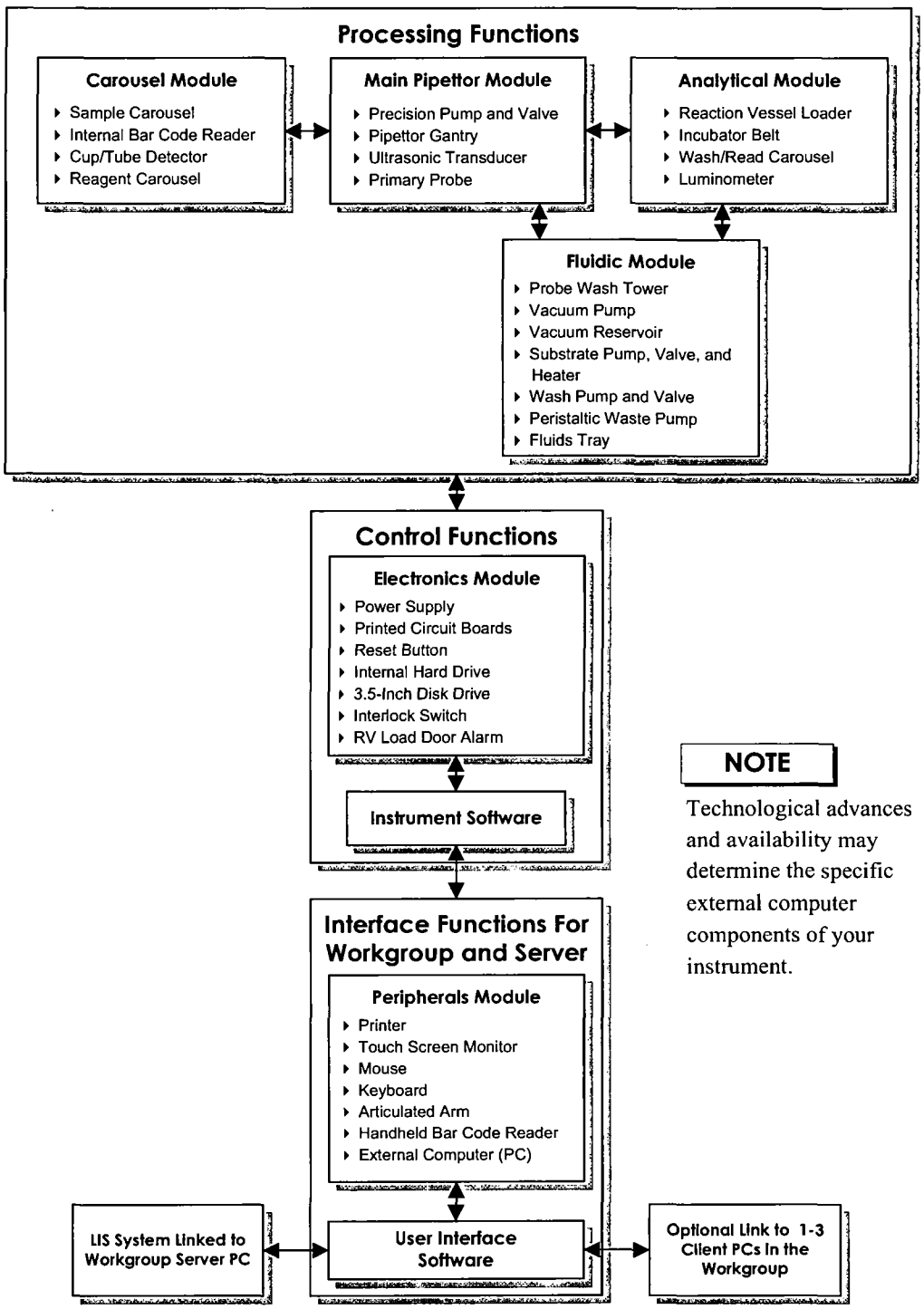
System Description



NOTE

Technological advances and availability may determine the specific external computer components of your instrument.

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System Modes

The Access 2 system has four system modes that indicate the operating state of the system. The current mode is displayed in the upper left corner of each screen. When the system is in the **Running** mode, the estimated completion time for the requested function displays as a text line above the three system command buttons.

Mode	Screen Display	Description
Ready		The system is ready to begin processing samples.
Running		The system is performing a function, such as processing samples, running a maintenance routine, or performing a diagnostic procedure.
Paused		The system continues current test processing, but no new tests are scheduled.
Not Ready		The system is not ready to process samples. The system is checking the status of subsystems, initializing motors, priming fluid lines, homing movable parts, warming necessary modules, or requires initialization.

System Status Buttons

The ten system status buttons are described below. Most buttons are color coded to alert you if a supply level requires your attention, a sample processing issue exists, or if the instrument has recorded a system event. Under normal operating conditions the button color will be neutral.

System Status Button	Button Colors
Wash Buffer Select to view the status of the wash buffer bottle. You can change the wash buffer bottle at any time during sample processing.	**Red** The wash buffer reservoir is almost empty, and no new tests can be scheduled. You must change the wash buffer bottle to continue processing tests.
Liquid Waste Select to view the status of the liquid waste bottle. You can change the liquid waste bottle at any time during sample processing.	**Red** The liquid waste bottle is full, and no new tests can be scheduled. You must change the liquid waste bottle to continue processing tests.

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System Status Button	Button Colors
Substrate Select to display the Supplies screen to check the level of on-board substrate, or change the substrate bottle. You can only change the substrate bottle while the system is in the **Ready** mode.	**Yellow** The system can process 60 or fewer test requests with the remaining substrate. Change the bottle at your next opportunity. **Red** The substrate bottle is empty, and no new tests can be scheduled. You must change the substrate bottle to continue processing tests.
Reaction Vessels (RVs) Select to display the Supplies screen to check on the RV supply, or load an RV cartridge. You can load RVs at any time during sample processing.	**Yellow** The system can process 60 or fewer test requests with the remaining RVs. Load an RV cartridge now, or at your next opportunity. **Red** The system can process 28 or fewer test requests with the remaining RVs, and no new tests can be scheduled. You must load an RV cartridge to continue processing tests.
RV Waste Bag Select to display the Supplies screen to check on the RV waste bag capacity, or change the RV waste bag.	**Yellow** The system can process 60 or fewer test requests with the remaining capacity in the waste bag. Change the RV waste bag at your next opportunity. **Red** The RV waste bag is full, and no new tests can be scheduled. You must change the waste bag to continue processing tests.
Quality Control Select to display the Quality Control screen to set up quality controls, or review quality control results.	**Red** A QC result is not within the acceptable range of expected values. You should review this result as soon as possible.
Event Log Select to display the Event Log screen for information about events generated by the Access 2 system. From the Event Log screen you can also display troubleshooting information about caution or warning events.	**Yellow** The system has generated a caution event that requires your attention. **Red** The system has generated a warning event, indicating a serious fault or error condition has occurred.

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System Status Button	Button Colors
Work Pending Select to display the Work Pending screen for information about samples for which the system cannot schedule tests. The Work Pending screen allows you to navigate to the Sample Manager screen to load samples or delete sample requests.	**Yellow** A sample required condition has occurred. You should load the required sample, or delete it from the work list.
Supplies Required Select to display the Supplies Required screen for information about supply and calibration conditions. You can correct most conditions from the Supplies Required screen.	**Yellow** The system requires supplies or calibration(s) to complete the requested tests.
Help Select to display specific information about the screen you are on, or to navigate to a picture with descriptions for the screen, to a list of related topics, or to any topic within *Help*.	The **Help** button color is always neutral.

System Command Buttons

You use the three system command buttons to run, pause, and stop the Access 2 instrument.

Button	Screen Display	Description
Run	Run	Select to process samples or run a maintenance routine.
Pause	Pause	Select to pause the instrument. The system stops pipetting after it finishes pipetting the current sample. Processing continues on samples already in progress.
Stop	Stop	Select to stop the instrument. The system stops processing and cancels any tests in progress.

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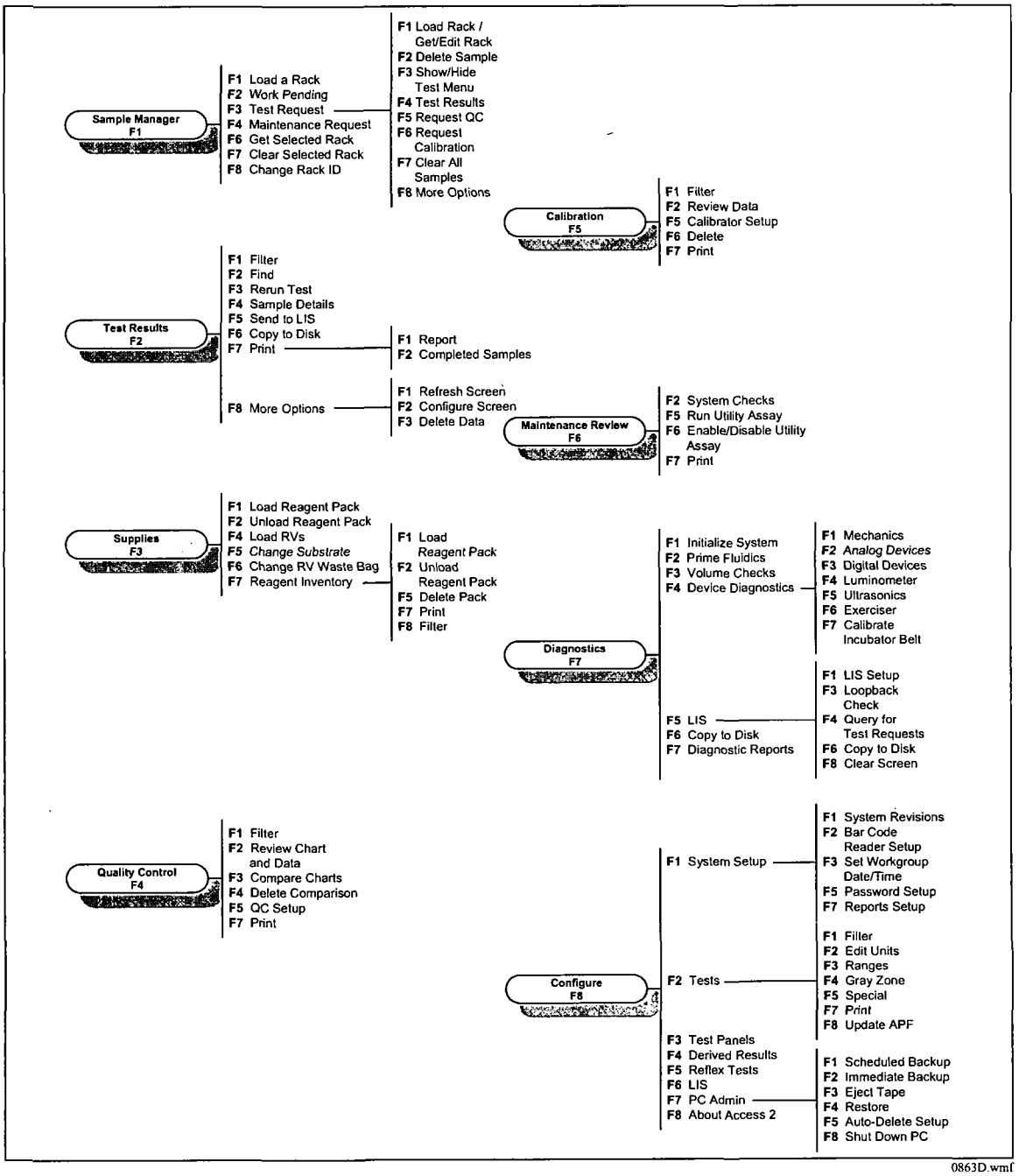
Main Menu Workflow

The Main Menu is the first screen you see when the system is installed or initialized. To get to this menu from any screen, press **Main Menu [F9]**. You can navigate everywhere through the Access 2 system using the eight function buttons across the bottom of the Main Menu.



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Precautions and Hazards

Safety Features

The Access 2 system is designed to meet U.S. and international safety standards. Safety labels are affixed to the instrument to alert you to safety considerations.

Interlock Switch

WARNING

Do not defeat the safety interlock switch on the cover.

The Access 2 system is equipped with an interlock switch to protect you from injury. If you open the front panel of the instrument, the interlock switch stops the movement of the main pipettor. Other mechanical devices will continue to operate with the front panel open. If you open the front panel while the system is processing samples, the system may cancel tests.

Safety Statements

The following statements describe general safety concerns.

WARNINGS

- **Reagents, calibrators, and controls used with the system may contain small quantities of sodium azide preservative. Sodium azide preservative may form explosive compounds in metal drain lines. Refer to National Institute for Occupational Safety and Health Bulletin: Explosive Azide Hazards (8/18/76).**
- **The Access 2 instrument has moving parts and uses high voltage in the ultrasonic transducer. Both present an injury hazard. You should not operate the Access 2 instrument with the covers open.**

CAUTION

Always plug the Access 2 system into a grounded three-conductor outlet. DO NOT bypass the grounding prong on the plug.

Safety Symbols

Symbol	Description
Attention Safety Symbol	A symbol with an exclamation point calls attention to important information to read, or is accompanied by another symbol indicating a particular safety hazard. The information is located either on the label with the symbol or in the Access 2 customer documentation. The text following the symbol provides additional information regarding safety conditions.

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Symbol	Description
Electrical Safety Symbol	The general electrical safety symbol indicates an electrical shock hazard. The luminometer contains a high voltage power supply that presents a shock hazard. The power supply does not contain operator-serviceable parts.
Biohazard Symbols	The biohazard symbols indicate areas of the instrument and associated fluid handling equipment that can contain potentially infectious human serum or blood products. Follow good laboratory practices in handling and disposing of materials from these areas.
Sharp Objects Symbol	The sharp objects symbol indicates areas of the instrument in which the skin can be punctured. **Do not put your hands in areas marked with this symbol while the instrument is running.**
Moving Parts Symbol	The moving parts symbol indicates areas of the instrument in which moving parts can cause injuries.
Electrostatic Discharge Symbol	The electrostatic discharge (ESD) symbol indicates areas of the instrument which can be damaged by static discharge.
Laser Symbol	The laser symbol indicates areas of the instrument where laser light is used. **Do not stare into the laser beam.**

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Disposal and Recycling

Symbol	Description
WEEE Directive	It is important to understand and follow all laws regarding the safe and proper disposal of electrical instrumentation. The symbol of a crossed-out wheeled bin on the product is required in accordance with the Waste Electrical and Electronic Equipment (WEEE) Directive of the European Union. The presence of this marking on the product indicates that the device: • was put on the European Market after August 13, 2005. • is not to be disposed via the municipal waste collection system of any member state of the European Union. For products under the requirement of WEEE directive, please contact your dealer or local Beckman Coulter office for the proper decontamination information and take-back program, which will facilitate the proper collection, treatment, recovery, recycling, and safe disposal of the device.
EU Battery Directive	Battery Safety and Disposal Instructions - Dispose of all batteries in accordance with local regulations. If you have any questions, please contact your local Beckman Coulter representative for information on the correct disposal or recycle programs for batteries. Beckman Coulter products can have two types of batteries. • User-Replaceable - Consult the product operating manual for battery replacement instructions. • Non-User-Replaceable - Please contact your local Beckman Coulter representative.
RoHS	The following labels and declarations meet the People's Republic of China Electronic Industry Standard SJ/T11364-2006 marking requirement for control of pollution caused by electronic information products.
	This logo indicates that this electronic information product contains certain toxic or hazardous substance or elements, and can be used safely during its environmental protection use period. The number in the middle of the logo indicates the environmental protection use period (in years) for the product. The outer circle indicates that the product can be recycled. The logo also signifies that the product should be recycled immediately after its environmental protection use period has expired. The date on the label indicates the date of manufacture.

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Symbol	Description
RoHS *(continued)*	This logo indicates that the product does not contain any toxic or hazardous substances or elements. The "e" stands for electrical, electronic and environmental electronic information products. This logo indicates that this electronic information product does not contain any toxic or hazardous substances or elements, and is green and is environmental. The outer circle indicates that the product can be recycled. The logo also signifies that the product can be recycled after being discarded, and should not be casually discarded.

Regulatory Symbols and Statements

The Access 2 instrument meets the requirements of a variety of domestic and international regulatory agencies, standards, and directives. This compliance is indicated by symbols and marks on the instrument, and by related statements in the system documentation.

Canadian Standards	The Canadian Standards Association (CSA) symbol indicates that the Access 2 Immunoassay System meets all U.S. and Canadian requirements for electrical safety.
CE Mark	A label with the CE mark of conformity signifies that the Access 2 Immunoassay System complies with applicable EU directives. The instrument Declaration of Conformity lists the directives with which the Access 2 system complies.
C-Tick Mark	The C-tick mark indicates that the instrument complies with applicable Australian Communications Authority requirements.

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Radio Frequency Emissions Statement

This IVD equipment complies with the emission and immunity requirements described in IEC 61326-2-6.

The Access 2 system has been tested and shown to be compliant with the requirements of CISPR 11 and part 15 of FCC rules for a Class A digital device. These requirements are intended to provide reasonable protection from interference when the instrument is operated in a commercial environment.

CAUTIONS

- **This equipment has been designed and tested to CISPR 11 Class A. In a domestic environment it could cause radio interference, in which case you may need to take measures to mitigate the interference.**
- **Prior to operation of this device, the electromagnetic environment should be evaluated. Do not use this device in close proximity to sources of strong electromagnetic radiation (for example, unshielded intentional RF sources) as these could interfere with proper operation.**
- **If you suspect interference between the Access 2 system and other equipment, you must take whatever action is required to correct the interference. Beckman Coulter suggests the following actions:**
  - **Move the equipment so there is a greater distance between the equipment and the Access 2 system.**
  - **Re-orient the equipment with respect to the Access 2 system.**
  - **Be sure the equipment is operating from a different power service connector than that of the Access 2 system.**

LED Safety Statement

The handheld bar code reader has been tested in accordance with EN60825-1 LED safety, and has been certified to be under the limits of a Class 1 LED device.

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System Specifications and Characteristics

Space Requirements

The dimensions of the instrument and the peripheral devices as of the date of this document are listed in the following table. The Access 2 system operates from a bench top. Be sure that the surface and surrounding area designated for these components is large enough to accommodate the system. For information about the printer, see the documentation provided by the local manufacturer.

Instrument	Width = 39 inches (99 cm) Height = 18.5 inches (47 cm) Depth = 24 inches (61 cm)
Instrument clearance required • Left clearance is for the fluids tray • Right clearance is for the monitor and keyboard on the articulated arm • Top clearance is measured from the bench top	Rear = 2 inches (5 cm) Left = 12 inches (30 cm) Right = 30 inches (76 cm) Top = 30 inches (76 cm)
External computer	Length = 13 inches (33 cm) Height = 4 inches (10 cm) Depth = 16 inches (41 cm)
Keyboard	Length = 18.25 inches (46 cm) Height = 1.38 inches (4 cm) Depth = 8.16 inches (21 cm)
Monitor	Width = 15 inches (38 cm) Height = 12.5 inches (32 cm) Depth = 3 inches (8 cm)

Instrument and Peripheral Device Weights

The weight of the instrument and the peripheral devices are listed in the following table. Be sure that the surface where these components will reside can support the system. For information about the printer, see the documentation provided by the local manufacturer.

Instrument (before supplies and samples added)	200 pounds (91 kg)
External computer	17.25 pounds (7.8 kg)
Monitor	12.5 pounds (5.5 kg)

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Operating Environment Requirements

The Access 2 system is for indoor use only and requires the following environmental conditions to operate properly:

Humidity	Operational: 20 to 80% Exposure: 10 to 80%
Maximum altitude	Operational: 6,500 feet (2,000 m) Exposure: 40,000 feet (12,200 m)
Temperature	Operational*,†: 64°F to 82°F (18°C to 28°C) Exposure: -22°F to 122°F (-30°C to 50°C)
Maximum ambient temperature change rate	3.6°F per 30 minutes (2°C)
Ambient light	Results not affected by ambient light levels between 0-200 foot-candles
Pollution degrees	According to IEC 664 definitions, the Access 2 system has been tested and shown to be operational at pollution degree 2

* Some assays require additional temperature restrictions. These restrictions are noted in the reagent instructions for use or in other communications from Beckman Coulter

† The operating environment temperature is influenced by factors such as room temperature, air circulation, heat sources near the system, and direct sunlight.

Electrical Requirements

The electrical line and any surge suppressors, backup power supplies (UPS units), and line conditioning transformers you use with the instrument must meet specific requirements.

Electrical Line

The electrical line supplies power to the Access 2 instrument. To avoid damaging the instrument, the electrical line should meet the following requirements:

Line power supply	115-120 volts alternating current (VAC) at 15 amps, or 220-240 VAC at 6 amps, at either 50 or 60 hertz (Hz), single phase power
Line dedication	Dedicated (Access 2 instrument is the only equipment connected to the electrical line)

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Line outlet	Located within 5 feet (1.5 m) of the Access 2 system **NOTE** The Access 2 system may be connected to a line conditioner. In this case, locate the line conditioner within 5 feet of the outlet.
Line protection device	Circuit breaker rated: • 15 amps (115-120 VAC line) • 6 amps (220-240 VAC line)
Line voltage fluctuations	Not to exceed ±10 VAC per cycle
Line voltage sags	Not to fall below: • 90 VAC at 15 amps • 180 VAC at 6 amps
Line voltage surges	Not to exceed: • 135 VAC at 15 amps • 250 VAC at 6 amps
Line voltage supplied to printer	See documentation provided by the manufacturer
Maximum voltage between neutral conductor and safety ground conductor	Not to exceed 2 VAC root mean squared (RMS)
Maximum resistance between the safety ground conductor and an accessible building safety ground	Not to exceed 0.1 ohm
Transient overvoltages	According to UL3101 Installation Category II

Electrical Current Consumption, Power Consumption, and Heat Production

The Access 2 components consume current and power, and produce heat at the following levels. For information about the monitor and printer, see the documentation provided by their manufacturers.

Component	Electrical Current Consumption	Power Consumption	Heat Production
Instrument	< 1.5 kilovolt amps (KVA)	800 watts	2,730 British Thermal Units/hour (BTU)
External computer	< 500 volt amperes (VA)	Not applicable	Not applicable

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Surge Suppressors

Beckman Coulter recommends that you do not use a surge suppressor with the Access 2 instrument. The instrument has built-in protection similar to that provided by a surge suppressor.

Beckman Coulter does recommend that you use a surge suppressor with the external computer, monitor, and printer. You should connect the surge suppressor to an outlet, not a line conditioner.

Instrument Line Conditioning Transformers

If you suspect you have alternating current (AC) power line problems, Beckman Coulter recommends that you connect the Access 2 instrument to a line conditioning transformer with local ground and high frequency isolation. If you use a line conditioning transformer, it should meet the following requirements:

Minimum output capacity	1,300 VA
Output voltage	120 or 240 VAC
Output frequency	50 or 60 Hz, single phase
Output wave form	True sine wave (< 5% distortion)
Output safety ground	Isolated local ground
Approvals	UL 1012, CSA C22.2 107.1 (UL 544, optional)

Instrument Backup Power Supplies (UPS Units)

If you want to use an uninterruptable power supply (UPS) unit as a backup power supply, Beckman Coulter recommends a UPS unit with local ground isolation. UPS units are designed to provide continuous AC power to equipment when the main AC power line is lost. These units use a standby battery with an AC inverter circuit to provide the required electrical output. Some units also provide various combinations of the protection features found in surge suppressors and line conditioning transformers. If your system is in a workgroup, the external computer acting as the server for your workgroup should be connected to a UPS unit. Your UPS unit should meet the following requirements:

Minimum output capacity	1,300 VA
Output voltage	120 or 240 VAC
Output frequency	50 or 60 Hz, single phase
Output wave form	True sine wave (< 5% distortion)
Standby runtime	Minimum 15 minutes at 1,000 watts output (low battery indicator and/or shutdown recommended)
Approvals	UL 1778, CSA C22.2 107.1 (UL 544, optional)

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Installation

The Access 2 instrument must be installed by a qualified Beckman Coulter technical support representative. Do not remove the instrument from the shipping crate until a technical support representative is present.

Warranty

The Access 2 Immunoassay System is covered by and subject to the provisions of the warranty included in your contractual agreement for the system or its reagents.

The customer is responsible for routine preventive maintenance procedures. Repairs arising from the failure to perform these maintenance procedures at the indicated time intervals will be made at the discretion of Beckman Coulter, and at the customer's expense.

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2 Shut Down and Restart

You can reboot the PC, the instrument, or both. Rebooting either one does not affect the other. You may use a reboot procedure in the following situations:

- The user interface (UI) is not responding correctly (PC reboot).
- You are directed to do so by a technical support representative or if you are following instructions in *Help* or in an Access 2 manual (PC and/or instrument reboot).

During the instrument rebooting process, the instrument system software is reset and a routine brings all devices to their home, or known, states. This routine is called initialization, and it prepares the system for further processing.

NOTES

- If you are rebooting both the PC and the instrument, you can reboot them in any order. For simplicity, the procedures instruct you to reboot the PC first, then the instrument.
- If you are rebooting an Access 2 PC that is a workgroup server, first you must shut down the other PCs (clients) in the workgroup. Next, restart the server PC. Finally, restart the client PCs.
- If you reboot only the PC, the instrument continues sample processing if it is in the **Running** mode. When the PC reestablishes communication with the instrument, the test data is automatically sent to the PC.

The instrument does not require periodic shutdowns. However, you should shut down the instrument before moving it or whenever the power will be turned off for an extended period of time (more than 5 days). Before shutting down the instrument, contact Technical Support to confirm your decision.

Rebooting the PC

To reboot the PC, you shut it down and then restart it. You do not need to reboot the instrument unless you are directed to do so. Use this procedure to reboot the PC.

Shutting Down the PC Under Normal Conditions

NOTE

If you are shutting down a workgroup server PC, you must shut down each of the client PCs in the workgroup first.

1. Go to the PC Admin screen. To get to this screen from the Main Menu, select **Configure F8** to display the Configure menu, then select **PC Admin F7**.
2. Select **Shut Down PC F8**. A confirmation message is displayed.

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3 Select **Yes F1** to shut down the PC.

If you are preparing to shut down the server, repeat step 1 through step 3 for each of the client PCs first. Then repeat step 1 through step 3 for the server.

4 Press and hold the PC power switch for at least 15 seconds to turn off the power to the PC.

5 Wait about 20 seconds, then perform the restarting procedure.

Shutting Down the PC When the UI is not Accessible

NOTES

- If the server UI is the only UI that is not accessible, shut down each of the client PCs. Then use this procedure to shut down the server.
- If a client UI is not accessible, use this procedure to shut down that client PC.

1 Simultaneously press the **[Ctrl]**, **[Alt]**, and **[Delete]** keys, then select **Shutdown**.

- If the keyboard does not respond, press the PC power switch to turn the power off.

2 Wait about 20 seconds, then perform the restarting procedure.

Restarting the PC

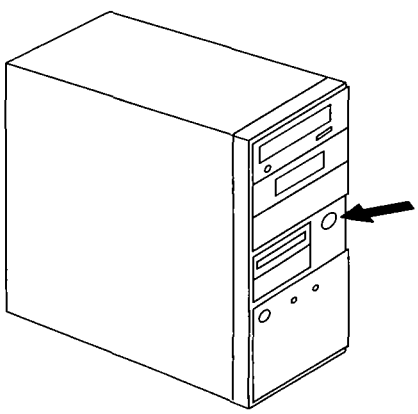
NOTE

If you are restarting multiple Access 2 PCs in a workgroup, restart the workgroup server first, then restart the client PCs.

1 Press the PC power switch to turn the power on.

2 Wait until the Main Menu screen appears before you continue normal operation.

If rebooting fails, contact Technical Support.



PC Power Switch

NOTE

If communication between the PC and the instrument is interrupted for an extended time (more than 30 minutes) while the instrument is processing tests, it may take a few minutes for test results to be sent to the PC after communication is reestablished. Do not use the system until the PC receives all the test results.

Go directly to the Test Results screen and filter the results by completion time. Watch the **Result** and **Comp. Time** columns. When it appears that the test results that were obtained while communication was interrupted have been transferred to the PC, you can continue normal operation.

If you have any questions, contact Technical Support.

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Rebooting the Instrument

Use this procedure to reboot the Access 2 instrument. There are two different ways to reboot the instrument:

- You can reboot using the reset button. This is also called a warm boot.
- You can reboot using the power switch. This is also called a cold boot.

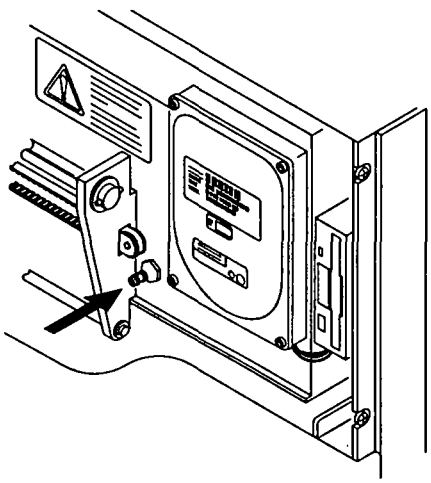
NOTES

- Do not select any buttons or press any keys until rebooting is complete. After you initiate a reboot, there is a pause of approximately 2 minutes as the software resets. Then the system enters the **Not Ready** mode and system initialization begins.
- During system initialization, the system homes mechanical devices and displays a flashing message in the system mode area. When most system devices complete initialization, the system changes to the **Ready** mode.
- The system continues to initialize the remaining devices and displays a flashing message in the system mode area. When the message disappears, system initialization is complete.
- If the system does not successfully initialize, contact Technical Support.

Rebooting Using the Reset Button

WARNING

You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.



Reset Button

1. Open the front panel of the instrument.
2. Locate the reset button, just to the right of the pipettor gantry.
3. Push and hold in the reset button for one second, then release.
4. Close the front panel of the instrument immediately.

NOTE

If the front panel remains open too long, the system cannot home the mechanical devices. If this occurs, press the reset button a second time, then close the front panel immediately.

5. Wait until the system is in the **Ready** mode and no message appears in the blue system mode area before you continue normal operation.

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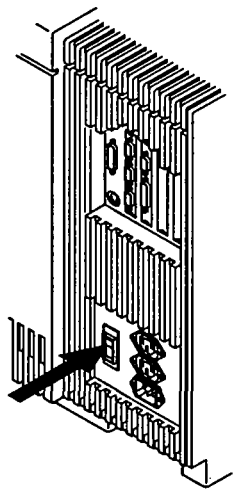
Rebooting Using the Power Switch

1. Be sure the front panel of the instrument is closed.
2. Locate the power switch on the lower, right side near the back of the instrument. Press the lower part of the switch to turn the power off (O position).
3. Wait about 20 seconds, then press the top part of the switch to turn the power on (| position).
4. Wait until the system is in the **Ready** mode and no message appears in the blue system mode area before you continue normal operation.



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Instrument Power Switch

Shutting Down the Instrument

Shut down the instrument only if you plan to move it or if the system power will be turned off for an extended period of time (more than 5 days). Before you shut down the instrument, contact Technical Support to confirm your decision.

WARNINGS

- **You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **If you are moving the instrument, make sure that the new location is properly plumbed. Reagents, calibrators, and controls used with the system may contain small quantities of sodium azide preservative. Sodium azide preservative may form explosive compounds in metal drain lines. Refer to *National Institute for Occupational Safety and Health Bulletin*: Explosive Azide Hazards (8/18/76).**

Use this procedure to shut down the Access 2 system.

1. Run the Special Clean routine.
2. Empty the liquid waste bottle.
3. If necessary, shut down the PC.
4. Locate the power switch on the lower, right side near the back of the instrument. Press the lower part of the switch to turn the power off (O position).

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Restarting the Instrument

Use this procedure to restart the instrument from a shutdown state.

WARNINGS

- **You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **Wash buffer contains ProClin* 300 preservative, which may cause sensitization by skin contact. After contact with skin, wash immediately with soap and water. Wear suitable gloves.**

NOTE

You must equilibrate the substrate used in this procedure to room temperature for the time specified in the reagent instructions for use before you load it onto the instrument. For detailed information, see the substrate reagent instructions for use .

Turning the Power On

1. If the PC was shut down, restart it.
2. Locate the power switch on the lower right side near the back of the instrument. Press the upper part of the switch to turn the power on (| position).
3. Wait until the system is in the **Ready** mode and no message appears in the blue system mode area before you continue the procedure.

   If initialization fails, review the Event Log and troubleshoot according to any error event with a similar date and time to the attempted initialization.

- ❑ (Optional, except following an extended shutdown) Prime the system fluidics.
- ❑ (Optional, except following an extended shutdown) Perform the probe volume checks.
- ❑ (Optional) Replenish supplies.
- ❑ (Optional, except following an extended shutdown) Run the Special Clean routine.
- ❑ (Optional, except following an extended shutdown) Run the System Check routine.

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3 Supplies

Changing the Wash Buffer Bottle

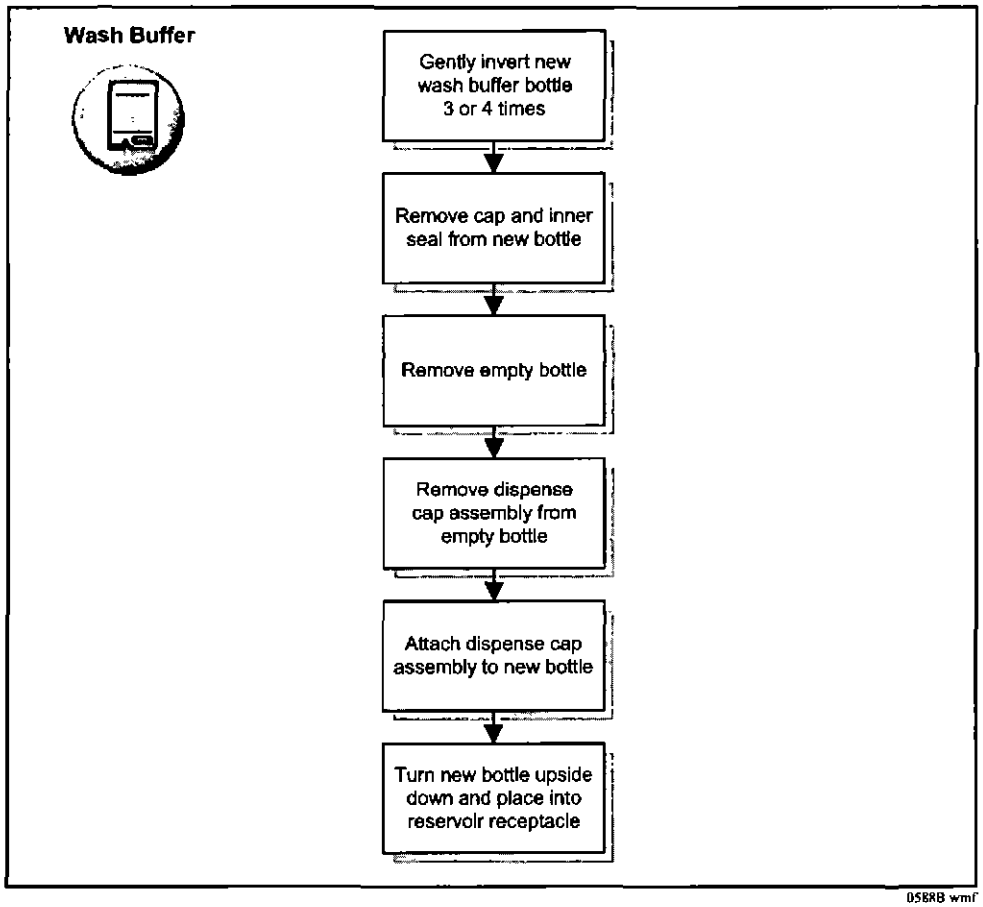
You can change the wash buffer bottle at any time. Because of the internal reservoir, the system continues processing samples even when you remove the wash buffer bottle. If you wait until the **Wash Buffer** button is red, the system schedules no new tests because the internal reservoir is almost empty.

WARNING

Wash buffer contains ProClin 300 preservative, which may cause sensitization by skin contact. After contact with skin, wash immediately with soap and water. Wear suitable gloves.

CAUTION

To avoid contaminating the wash buffer, do not touch any part of the dispense cap assembly that enters the reservoir. Handle the dispense cap assembly only by the screw cap, not the nozzle.



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Changing the Liquid Waste Bottle

The **Liquid Waste** button turns red when the waste bottle is full. The system will not schedule any new tests until you change the liquid waste bottle. You can change the liquid waste bottle any time, even during processing, and preferably before it is full. The **Liquid Waste** button does not turn yellow.

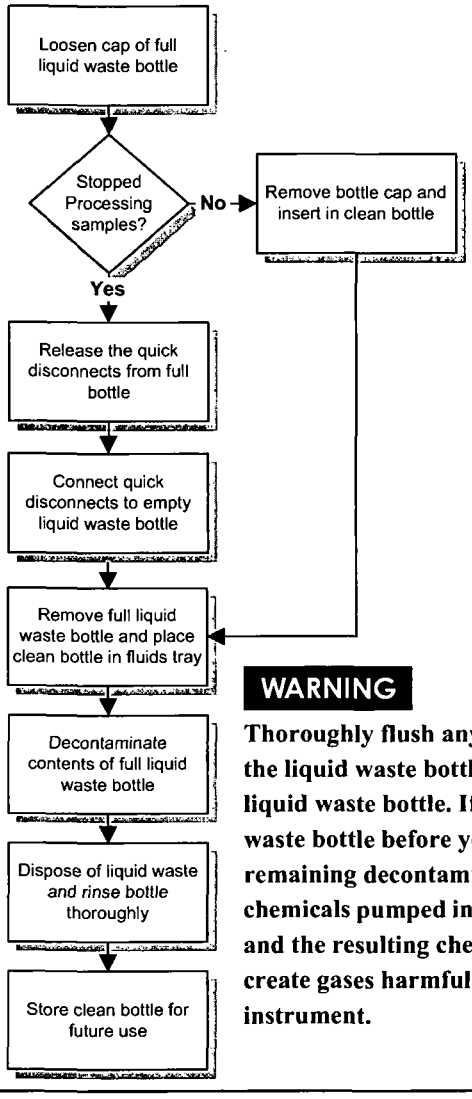
WARNING

You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazardous materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.

Liquid Waste

NOTE

The liquid waste drain kit may be used to replace the waste bottle and to direct liquid waste to a floor drain. As site conditions vary, Beckman Coulter requires that you consult with Technical Support to determine whether your system can be fitted with the kit.



WARNING

Thoroughly flush any decontaminant from the liquid waste bottle before you store the liquid waste bottle. If you reinstall the liquid waste bottle before you flush it, any remaining decontaminants may react with chemicals pumped into the liquid waste bottle and the resulting chemical reactions can create gases harmful to you or the instrument.

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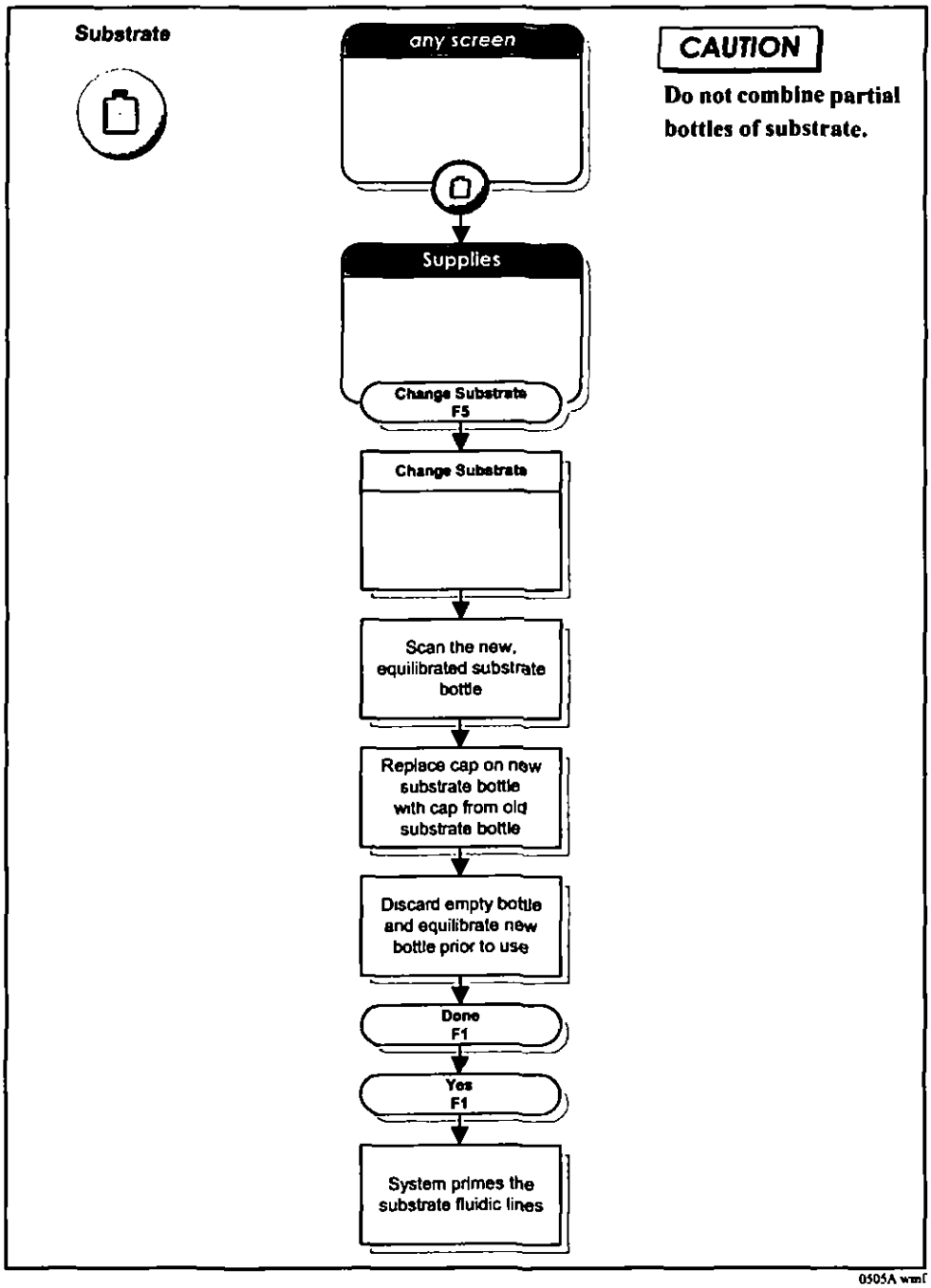
Changing the Substrate Bottle

When the system can process 60 or fewer tests with the current supply of substrate, the **Substrate** button turns yellow. When the substrate bottle is empty, the button turns red, and the system cannot start processing samples until you connect a new bottle of substrate. You can only change the substrate bottle while the system is in the **Ready** mode.



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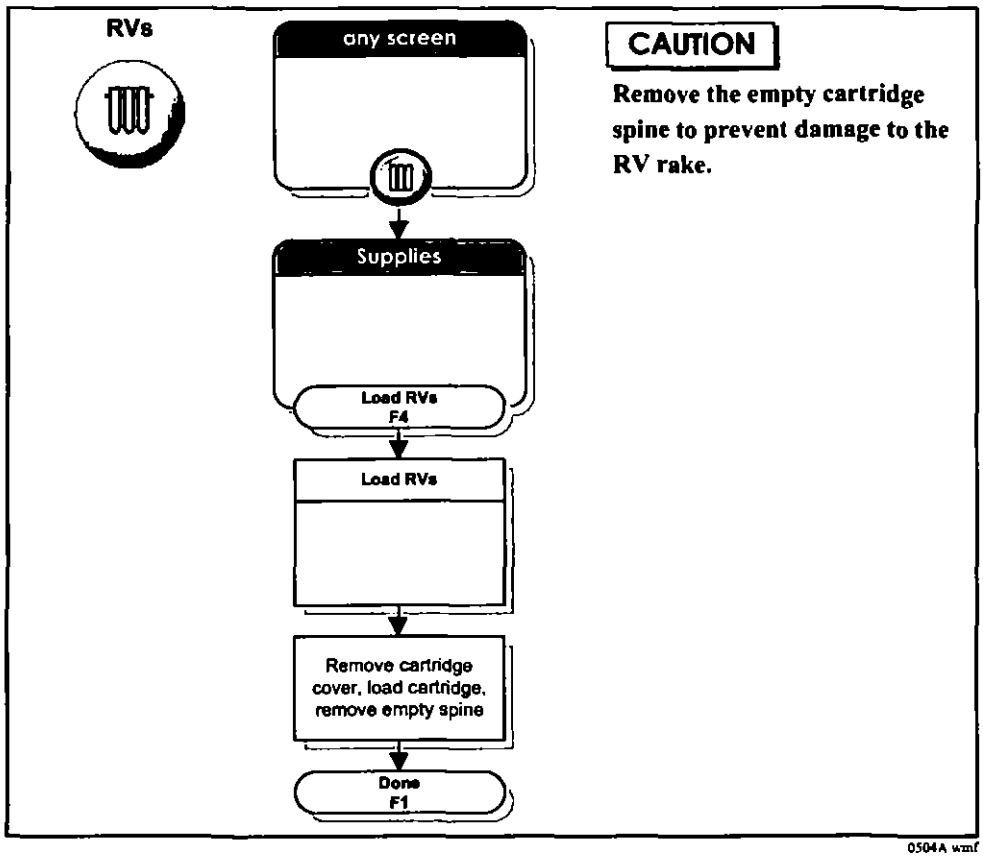
Loading Reaction Vessels (RVs)

During an Access 2 test, the chemical reaction occurs in a container called a reaction vessel (RV). Each test uses one or two RVs.

- When there are 60 or fewer RVs available, the **RVs** button turns yellow.
- When there are 28 or fewer RVs available, the **RVs** button turns red.
- When no RVs are available, the system cannot process another sample until you load a new RV *cartridge onto the instrument.*

NOTES

- You can load only full cartridges of RVs. If you try to load RVs when the instrument only has room for a partial cartridge, the system displays a message.
- If the system is processing samples and has one row or fewer RVs left when you try to load more, the system displays a message. *You must wait until the instrument* stops before you load the new cartridge.
- RVs can fall between the rake and the wall of the incubator if you do not load RVs properly by *selecting* ***Load RVs F4*** *from the Supplies or Supplies Required screen.*
- To be sure that all 98 RVs are firmly seated in the cartridge spine, press down on the spine before you load the cartridge.



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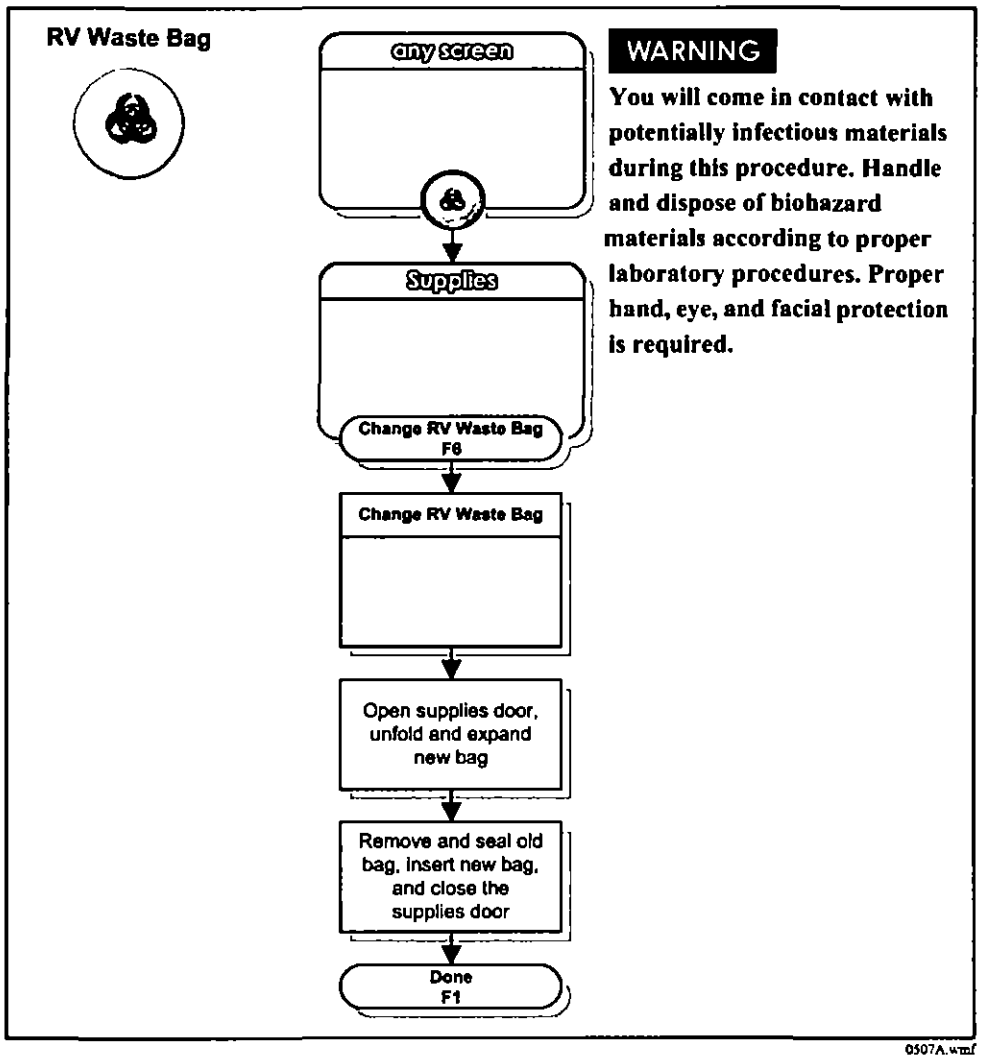
Changing the Reaction Vessel Waste Bag

When the waste bag has room for 60 or fewer RVs, the **RV Waste Bag** button (represented by a biohazard symbol) turns yellow. When the RV waste bag is full, the button turns red and the system will not start processing samples. You must change the RV waste bag.

CAUTIONS

- **If the system is in the Running mode when you change the RV waste bag, the system may try to eject an RV when the plastic collar on the waste bag is blocking the ejection chute. This will cause a jam.**
- **To prevent damaging the system, DO NOT push an RV that is sticking out from the ejection chute all the way back into the chute.**



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Loading a Reagent Pack

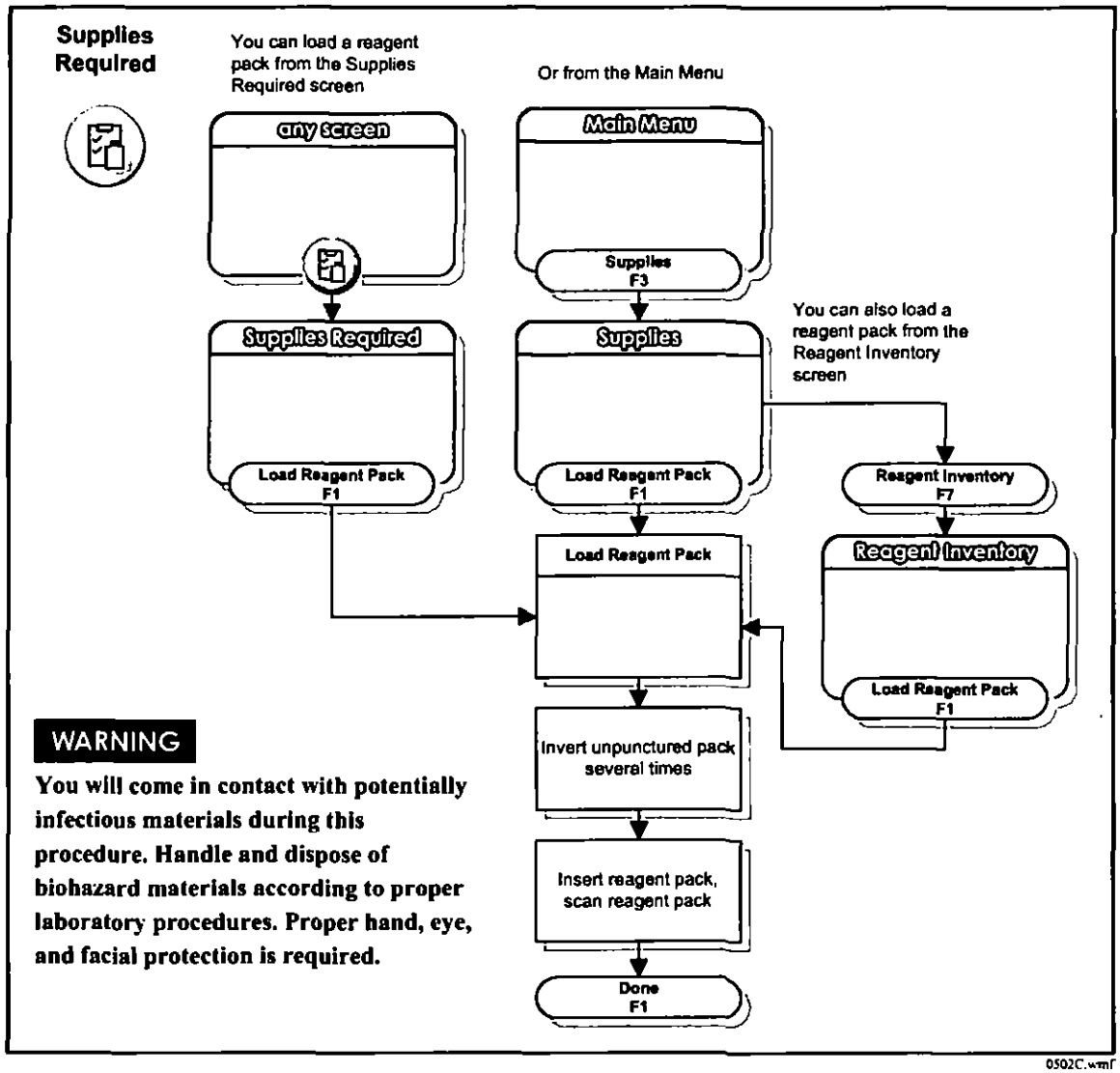
When an on-board reagent pack does not contain enough reagent to process requested tests, the system assigns those tests the Supplies Required status and the **Supplies Required** button (represented by a checklist) turns yellow.

WARNING

If you are reloading a partially used reagent pack, it must be returned to the same stand-alone system or Access 2 workgroup from which it was removed. If a partially used reagent pack is loaded on a different system or workgroup, it will be inventoried as a full pack and inaccurate results may occur.

CAUTION

To prevent damaging the reagent pack, be sure it is properly seated in the reagent carousel.



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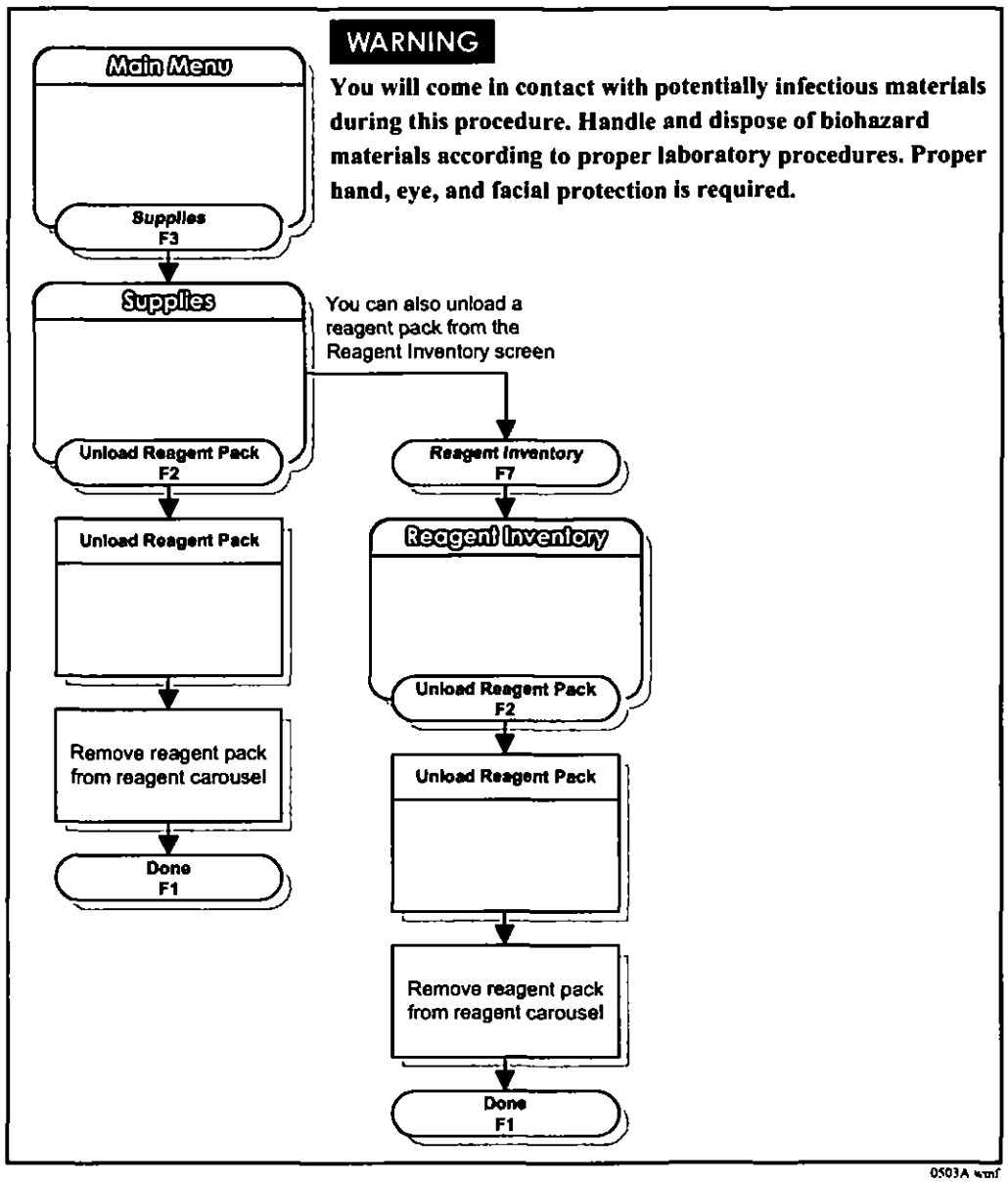
Unloading a Reagent Pack

Use this procedure to unload a reagent pack from the instrument.

NOTES

- If the system is using a reagent pack to process tests, you cannot unload it (identified by the in-use [padlock] icon on the Supplies screen).
- When you unload a partially full reagent pack, the system keeps track of the number of tests left in the pack until you reload it or manually delete it from inventory.
- Immediately unload any empty reagent packs.



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Retrieving Misplaced Reagent Packs

For the Access 2 system to accurately track the proper locations of reagent packs on the reagent carousel, the packs must be loaded and unloaded using the appropriate system windows. If you load a pack and do not use the Load Reagent Pack window, or if you use the Unload Reagent Pack window, but do not remove the pack, you will have a misplaced pack on your system.

Use this procedure to retrieve a misplaced reagent pack.

WARNING

You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.

1. Be sure the system is in the **Ready** or **Not Ready** mode, and then unload all reagent packs from the reagent carousel.
2. Go to the Mechanics screen. To get to this screen from the Main Menu, select **Diagnostics F7** to display the Diagnostics menu, then

   Select **Device Diagnostics F4** to display the Device Diagnostics screen, then

   Select **Mechanics F1**.
3. Select **Disable Motors F8**.
4. Slide the carousel door to the left to open it, and then open the reagent carousel door.
5. Gently turn the reagent carousel one rotation. If you find any reagent packs remaining on the carousel, remove them as they come into position at the reagent carousel door.
6. After verifying that all packs are removed, close the reagent carousel door and then slide the carousel door to the right to close it.
7. Select **Enable Motors F8**.
8. Home the reagent carousel.
9. When homing is complete, initialize the system.
10. When system initialization is complete, reload all of the packs you removed from the reagent carousel.

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4 Racks and Sample Containers

Racks

To accommodate sample containers of different sizes, the instrument uses three types of racks:

- 13 mm (for 12 mm and 13 mm sample tubes)
- 16 mm elevated (for 16x75 mm sample tubes)
- 16 mm (for 16x100 mm sample tubes)

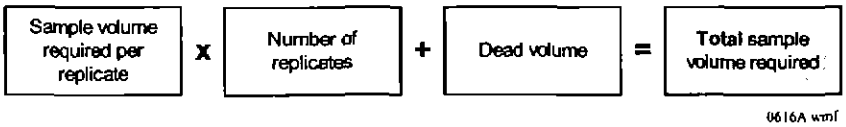
Racks are identified by a bar code label. When the instrument scans the rack bar code label, it identifies the type of sample containers in the rack and determines the appropriate pipetting depth for aspirating sample.

CAUTION

Only load sample containers on a rack with the appropriate ID.

Calculating Sufficient Sample Volume

To be sure the sample volume is sufficient for the tests to be run, calculate the total volume of sample needed for the sample container by using this equation:



NOTES

- To find the sample volume required per replicate, see the reagent instructions for use.
- Dead volume is the amount of sample in the bottom of a sample container that is required to be sure that enough sample is available for the instrument to complete an assay.

WARNING

If you use tubes with separator gel, be sure that the tube contains sufficient sample volume. Insufficient sample volume may cause the instrument to attempt to aspirate the separator gel, which can damage the instrument and compromise the integrity of the test results.

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Sample Containers

Place all samples to be tested on the Access 2 system in racks before loading them onto the instrument. The rack ID on each rack identifies what type of sample containers you may use in that rack. Each rack holds up to ten sample containers. Place all sample containers except insert cups directly in the rack. Place insert cups into another sample container appropriate for the rack you are using.

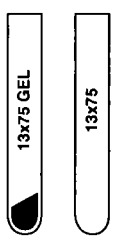
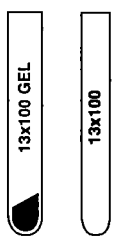
WARNINGS

- **You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **Air bubbles in samples can affect level sensing by the Access 2 system and compromise the integrity of the test results. Avoid creating bubbles when transferring samples to a secondary container. Always inspect samples before loading on the analyzer, and remove or break any bubbles.**
- **Use only recommended sample containers and place them in a rack with a rack ID defined for that type of sample container. Using containers other than those specified for use with a particular rack ID may damage the system and compromise the integrity of test results.**

The following table lists all of the sample containers you can currently use on the Access 2 instrument, the corresponding rack ID range and the dead volume for each container.

WARNINGS

- **You must have a sufficient volume of sample to process the tests you requested. To be sure you have enough sample, calculate the total volume needed for the sample container using the Calculating Sufficient Sample Volume procedure in this section. If you do not follow the provided procedure, sample processing problems may occur without warning.**
- **Remove caps from all sample containers before loading on the Access 2 system.**

Sample Container Information	Bar Code Label Icon	Sample Container Information	Bar Code Label Icon
13x75 mm Tube with or without separator gel • Border: Lime green • Rack IDs: 1300 - 1399 • Dead Volume: 500 µL • Sample rack: 13 mm NOTE: 13x75 mm tubes may also be used with Rack IDs 1 - 99 or 800 - 899, at a Dead Volume of 3.4 mL.		13x100 mm Tube with or without separator gel • Border: Forest green • Rack IDs: 1400 - 1499 • Dead Volume: 3.0 mL • Sample rack: 13 mm NOTE: 13x100 mm tubes may also be used with Rack IDs 1 - 99 or 100 - 199, at a Dead Volume of 4.9 mL.	

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Sample Container Information (continued)	Bar Code Label Icon	Sample Container Information	Bar Code Label Icon
12x75 mm Tube with or without separator gel • Border: Lime green • Rack IDs: 1300 - 1399 • Dead Volume: 500 µL • Sample rack: 13 mm NOTE: 12x75 mm tubes may also be used with Rack IDs 1 - 99, at a Dead Volume of 3.4 mL.	12x75	16x100 mm Tube with or without separator gel • Border: Midnight blue • Rack IDs: 1500 - 1599 • Dead Volume: 4.5 mL • Sample rack: 16 mm NOTE: 16x100 mm tubes may also be used with Rack IDs 900 - 999, at a Dead Volume of 7.6 mL.	16x100 GEL 16x100
16x75 mm Elevated Tube • Border: Purple • Rack IDs: 1000 - 1099 • Dead Volume: 700 µL • Sample rack: 16x75 mm ELEV	16x75	Beckman Coulter Access 3.0 mL Sample Container • Border: Red • Rack IDs: 500 - 599 • Dead Volume: 150 µL • Sample rack: 13 mm or 16 mm	
Beckman Coulter Access 2.0 mL/13 mm Sample Cup • Border: Dark green • Rack IDs: 1 - 99 or 400 - 499 (only 400 - 499 have the icon) • Dead Volume: 150 µL • Sample rack: 13 mm	2.0 mL	Beckman Coulter Access 1.0 mL/13 mm Insert Cup in 13x100 mm Tube • Border: Blue • Rack IDs: 600 - 699 • Dead Volume: 400 µL • Sample rack: 13 mm	13x100
Beckman Coulter Access 1.0 mL/13 mm Insert Cup in 13x75 mm Tube • Border: Light green • Rack IDs: 700 - 799 • Dead Volume: 300 µL • Sample rack: 13 mm	13x75	Beckman Coulter 0.5 mL Sample Cup • Border: Light pink • Rack IDs: 2500 - 2599 • Dead Volume: 80 µL • Sample rack: 13 mm	0.5 mL
Beckman Coulter Auto Aliquot Tube (use only Beckman Coulter P/N 2910034) • Border: Purple • Rack IDs: 1600 - 1699 • Dead Volume: 400 µL • Sample rack: 13 mm	Autoaliquot	Beckman Coulter Access 2.0 mL/16 mm Insert Cup in 16x100 mm Tube • Border: Orange • Rack IDs: 200 - 299 • Dead Volume: 400 µL • Sample rack: 16 mm	16 mm

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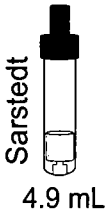
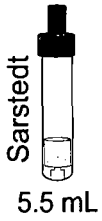
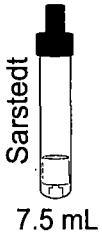
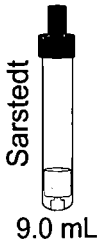
Sample Container Information (continued)	Bar Code Label Icon	Sample Container Information	Bar Code Label Icon
Beckman Coulter Pediatric Insert Cup in a Beckman Coulter Pediatric Tube Adapter • Border: Pink • Rack IDs: 1800 - 1899 • Dead Volume: 100 µL • Sample rack: 13 mm		Sarstedt S-Monovette* Tube 90x13 mm 4.9 mL • Border: Dark brown • Rack IDs: 2100 - 2199 • Dead Volume: 3 mL • Sample rack: 13 mm	
Sarstedt S-Monovette Tube 75x15 mm 5.5 mL • Border: Red-brown • Rack IDs: 2200 - 2299 • Dead Volume: 3.6 mL • Sample rack: 16x75 mm ELEV		Sarstedt S-Monovette Tube 92x15 mm 7.5 mL • Border: Light brown • Rack IDs: 2300 - 2399 • Dead Volume: 5 mL • Sample rack: 16x100 mm	
Sarstedt S-Monovette Tube 92x16 mm 9 mL • Border: Gray-brown • Rack IDs: 2400 - 2499 • Dead Volume: 6 mL • Sample rack: 16x100 mm			

* Monovette is a trademark of Sarstedt A.G. & Co.

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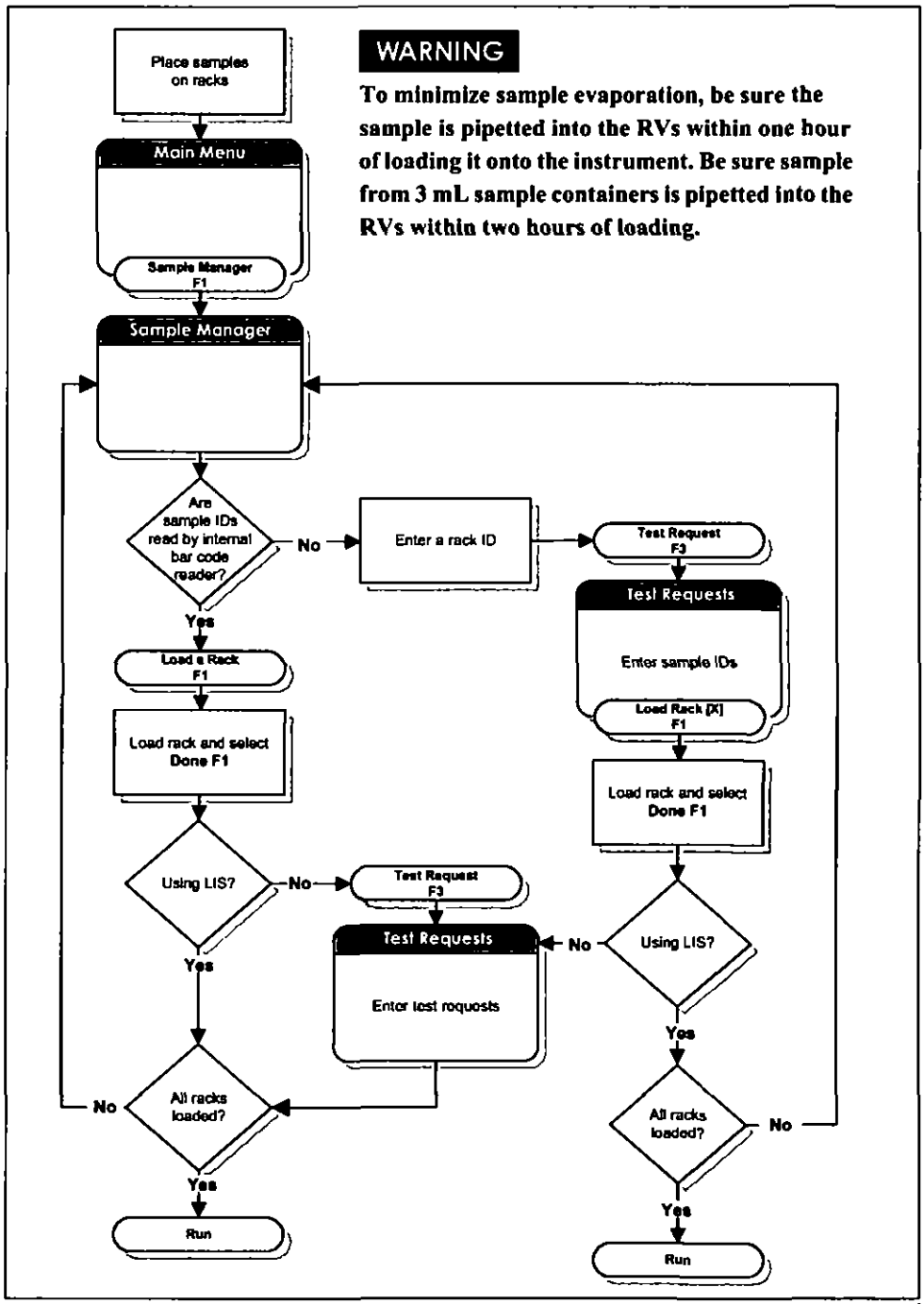
5 Sample Manager

Sample management is the process of placing patient, maintenance, quality controls, or calibration samples in racks, entering test requests, and loading the racks onto the Access 2 instrument for processing.



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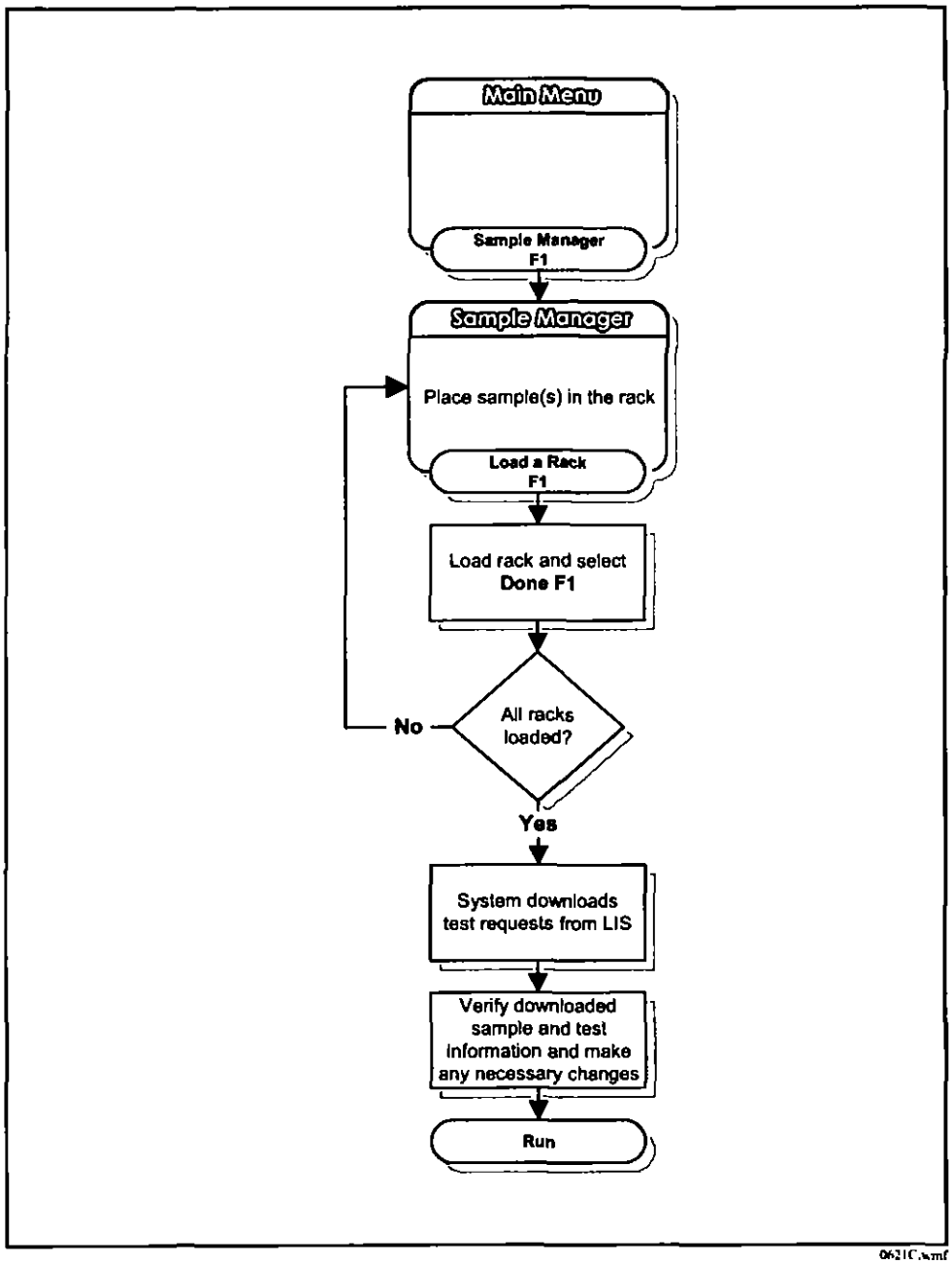
Processing LIS Patient Test Requests

If you are using bar-coded sample containers and are downloading test requests from an LIS, use this procedure to load racks and run the tests. You can load up to six racks at one time.



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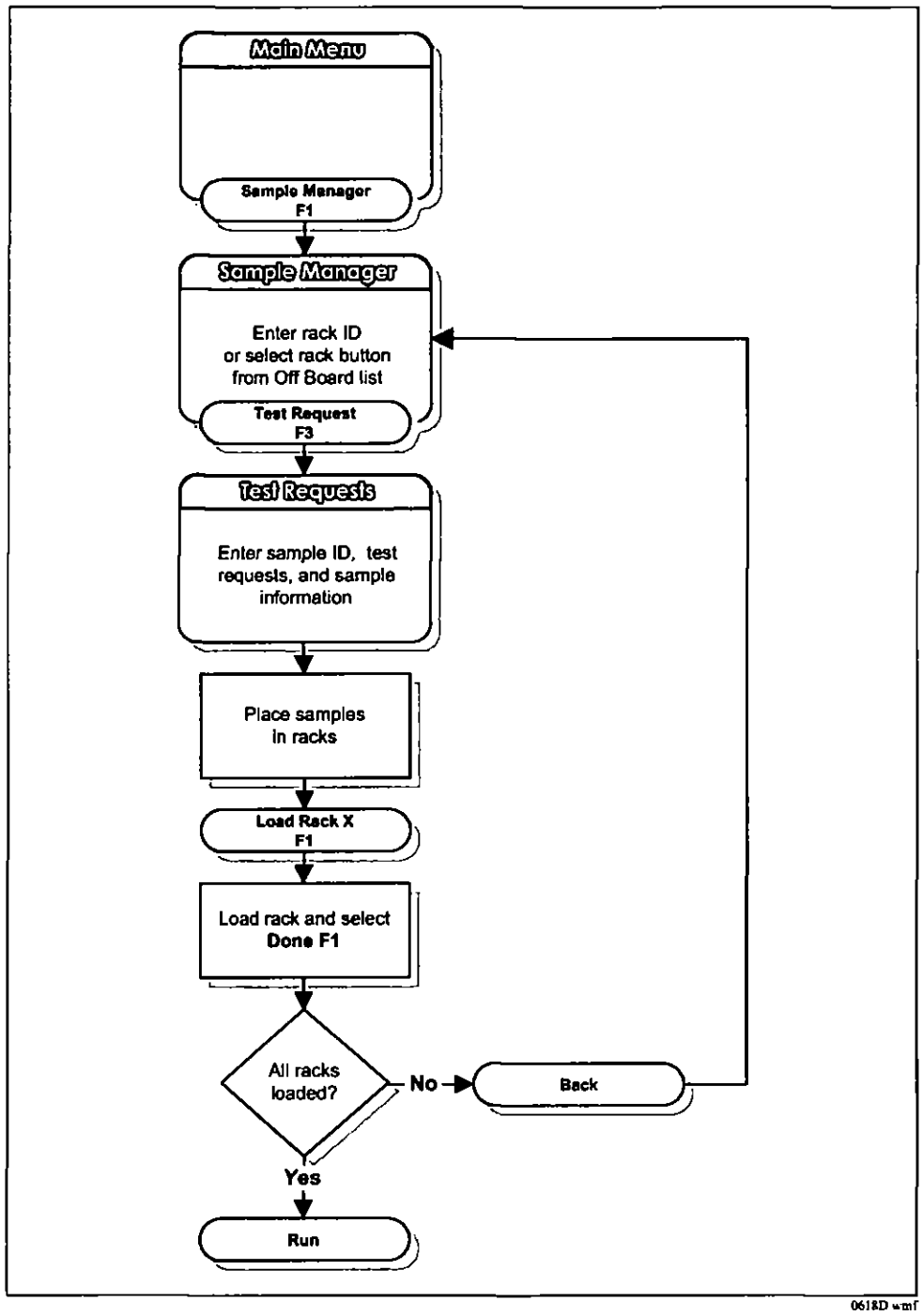
Entering Patient Test Requests Manually

If you have disabled sample bar code scanning, or need to enter test requests and sample information manually, use this procedure to manually enter test requests.



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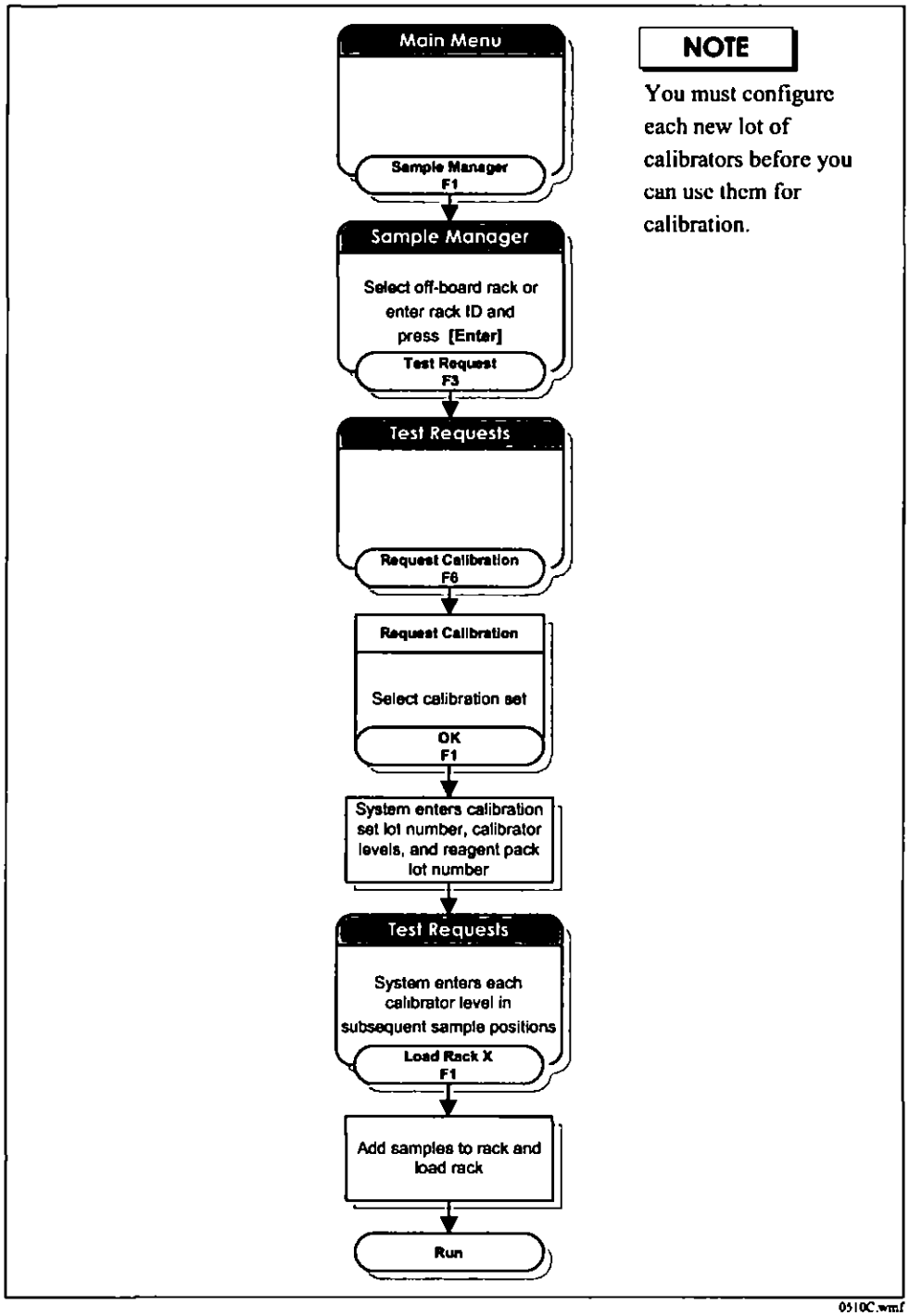
Entering Calibration Test Requests

You run a calibration by setting up a set of calibrators specific for an assay or group of assays. Each calibration is associated with a specific reagent pack lot number.



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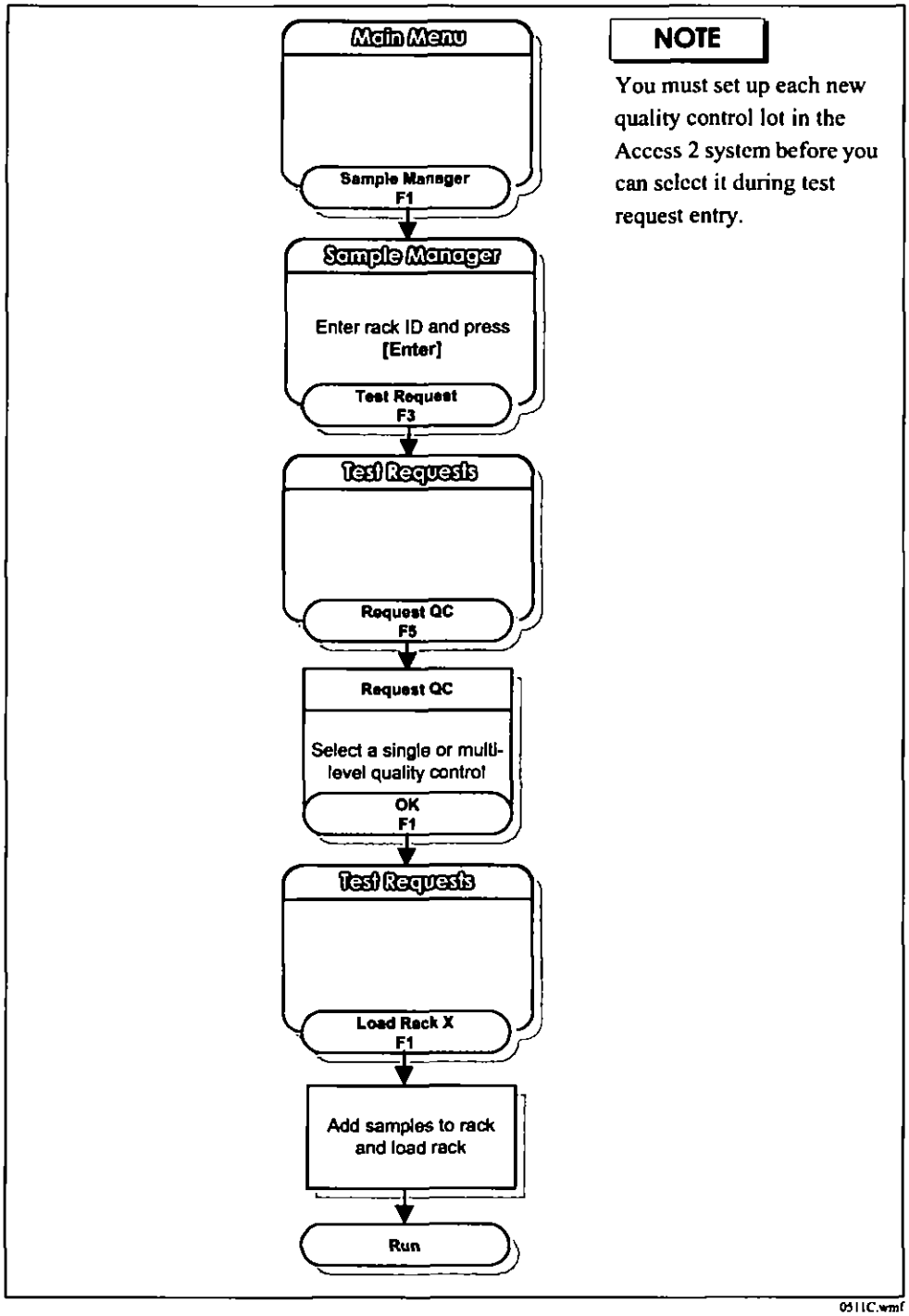
Entering Quality Control Test Requests

You run quality controls by entering a quality control test request for a quality control sample or set of samples. When you enter a quality control test request, you select a specific quality control lot number from the Request QC window.



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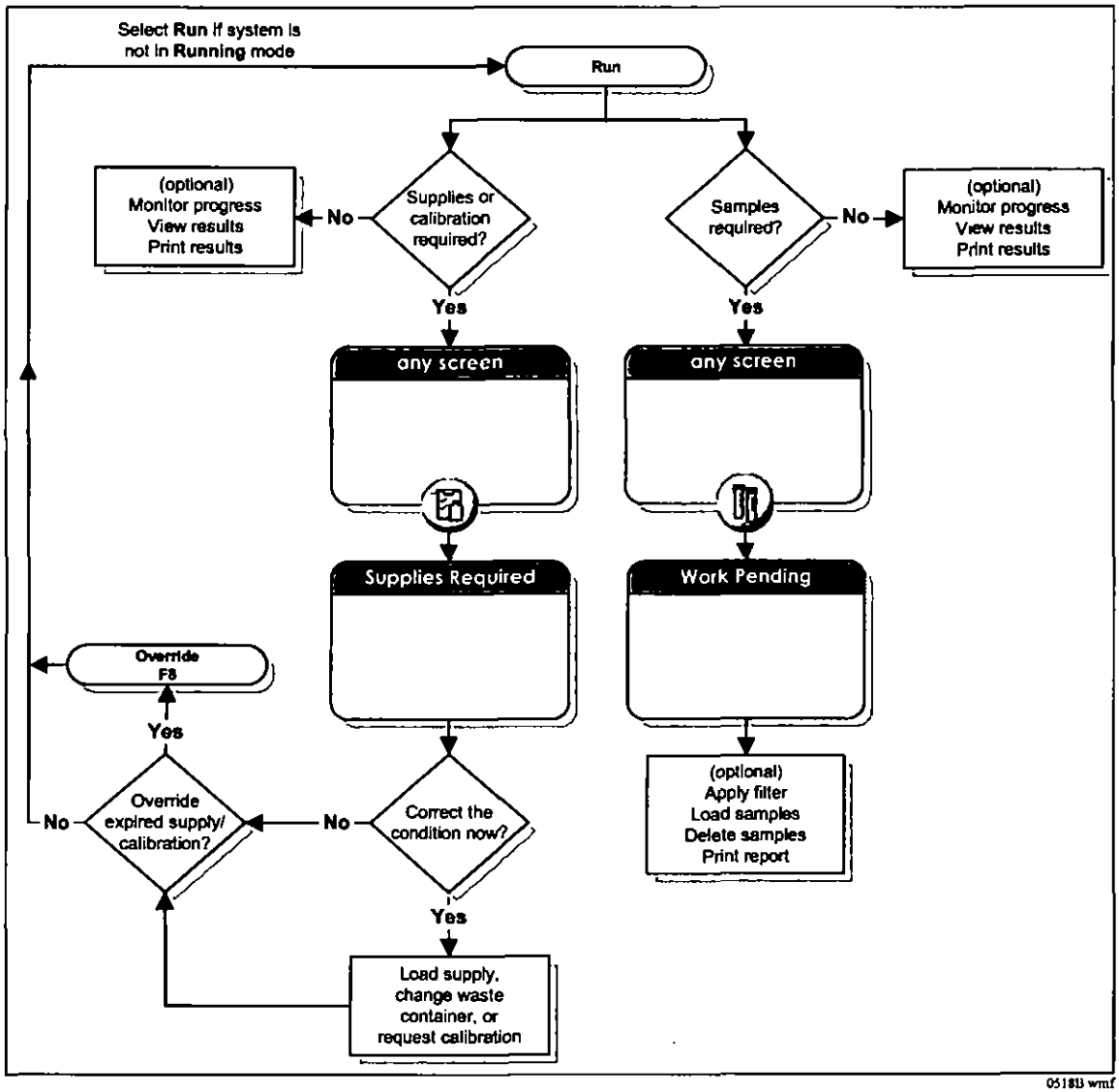
Processing Samples

Sample processing begins after you verify supplies, load samples, and enter or verify test request information. Select **Run**.



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6 Maintenance

Daily Maintenance

In order to keep the Access 2 system running properly, perform daily maintenance once every 24 hours.

NOTES

- If you use the Access 2 system to process the Vitamin B_{12} assay, you should also run the Special Clean routine at the end of every day or whenever the instrument will not process samples for 8 hours or more. For more information about performing the Special Clean routine, see the *Help* system.
- If the system is not used to run assays every day, it is still important to perform daily maintenance on schedule to ensure that the system is ready when needed.

WARNINGS

- **You will come in contact with potentially infectious materials during these procedures. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **Citranox cleaning solution is acidic and may cause eye or skin irritation. See the manufacturer's label for details.**
- **Contrad 70 cleaning solution is alkaline and may cause severe eye irritation or mild skin irritation. See the manufacturer's label for details.**

Required Materials

- Fiber-free polyester swabs (or equivalent fiber-free applicators)
- *Maintenance Log (see the Maintenance Log in this section)*
- 13 mm rack for 2 mL sample cups; the rack must have a rack ID between 1-57 or 400-456
- Wash buffer (or deionized water)
- Citranox* cleaning solution
- Contrad** 70 cleaning solution
- 2.0 mL sample cups (three cups)

WARNING

Wash buffer contains ProClin 300 preservative, which may cause sensitization by skin contact. After contact with skin, wash immediately with soap and water.
Wear suitable gloves.

NOTE

Use only the 2.0 mL sample cups when performing the maintenance routines. Using any other sample containers may result in level sensing errors and cancellation of the maintenance routine.

CAUTIONS

- **Be sure not to bend or damage the fragile probe tips.**
- ***To avoid contamination*, use a new applicator on each type of probe.**
- **Do not wipe the tip of the probe. Fibers on or inside the probes can clog the probes or valves in the fluidic module.**

* Citranox is a trademark of Alconox, Inc.
** Contrad is a trademark of Decon Laboratories, Inc.

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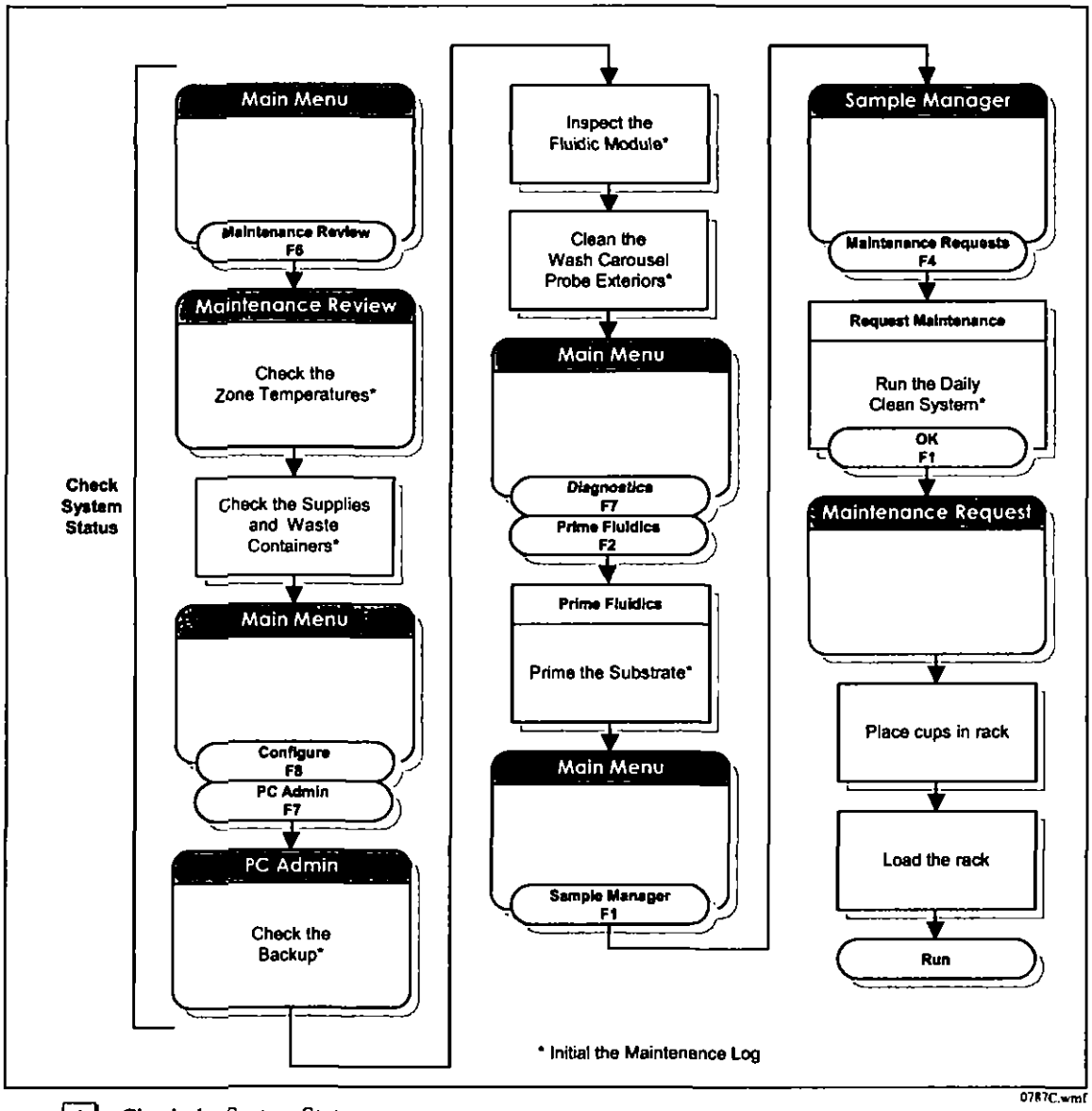
Daily Maintenance Steps



1. Check the System Status
2. Inspect the Fluidic Module
3. Clean the Wash Carousel Probe Exteriors
4. Prime the Substrate
5. Run the Daily Clean System Routine

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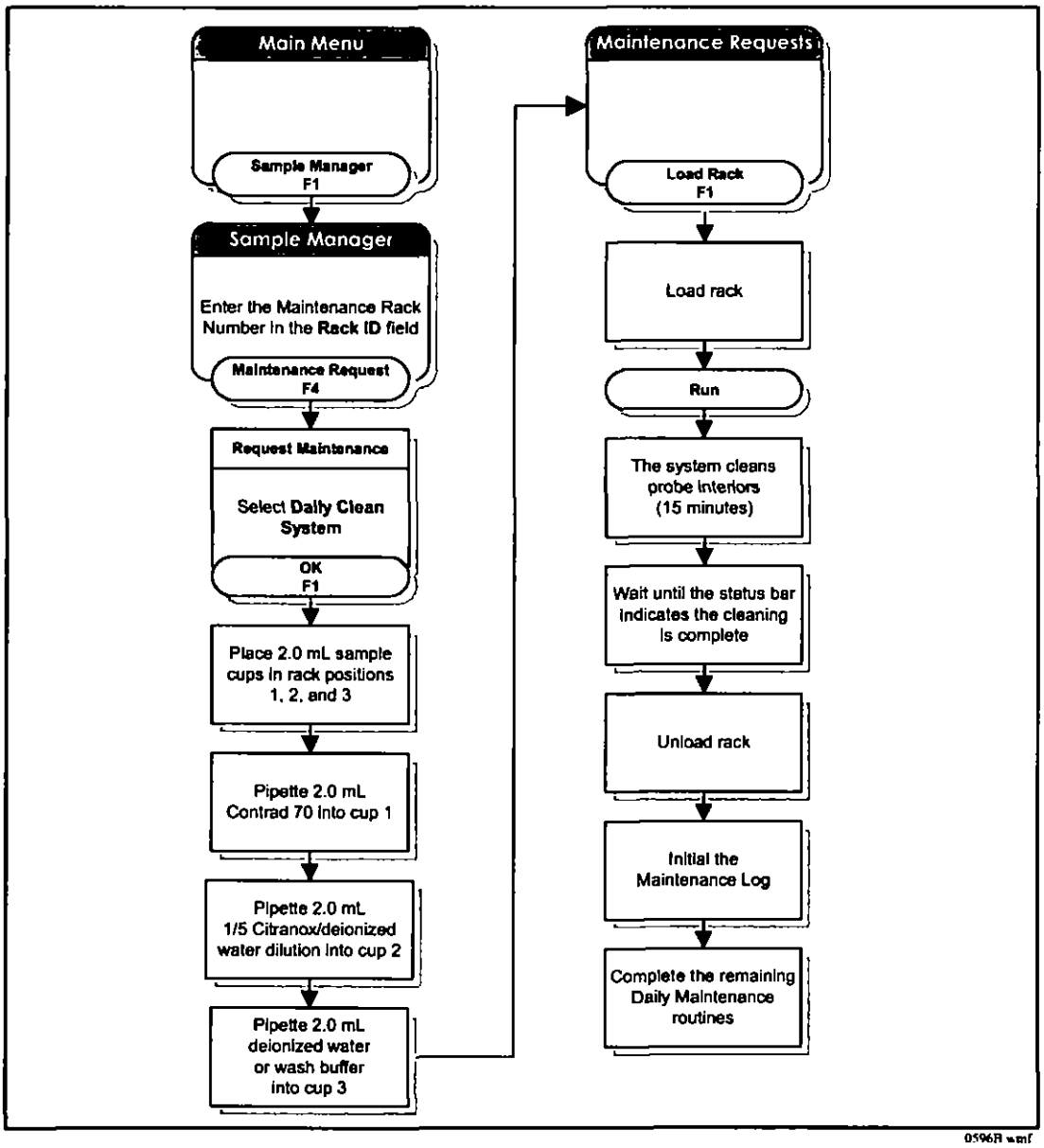
Daily Clean System Routine

WARNINGS

- **You will come in contact with potentially infectious materials during these procedures. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **Unless there is an emergency, let the maintenance routine run to completion. Cancelling the routine may damage the instrument and compromise the integrity of subsequent test results.**
- **If you cancel the routine, do not initialize the system. Contact Technical Support for assistance.**



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Weekly Maintenance

In order to keep the Access 2 system running properly, perform weekly maintenance once every seven days.

NOTE

If the system is not used to run assays every day, it is still important to perform weekly maintenance on schedule to ensure that the system is ready when needed.

WARNINGS

- **Methanol is extremely flammable. Do not use near heat or flame. Do not ingest. Avoid contact with eyes, skin, and clothing. Use with adequate ventilation.**
- **Contrad 70 cleaning solution is alkaline and may cause severe eye irritation or mild skin irritation. See the manufacturer's label for details.**
- **Wash buffer contains ProClin 300 preservative, which may cause sensitization by skin contact. After contact with skin, wash immediately with soap and water. Wear suitable gloves.**

Required Materials

- Lint-free cloth
- Deionized or distilled water
- Maintenance Log (see the Maintenance Log in this section)
- Spare liquid waste bottle (as needed)
- Spare waste filter bottle (as needed)
- Alcohol or alcohol swabs or wipes (methanol can be substituted for cleaning the exterior of the aspirate probes)
- Proper hand, eye, and facial protection for handling biohazardous materials
- Clean aspirate probes (three)
- Contrad 70 cleaning solution
- Beakers (two)
- Aspirate Probe Cleaning Kit (3.0 mL syringe, disposable aspirate probe brush, aspirate probe syringe fitting assembly consisting of a fitting and tubing)
- Disposable aspirate probe brushes (as needed)
- Absorbent paper
- Wash buffer

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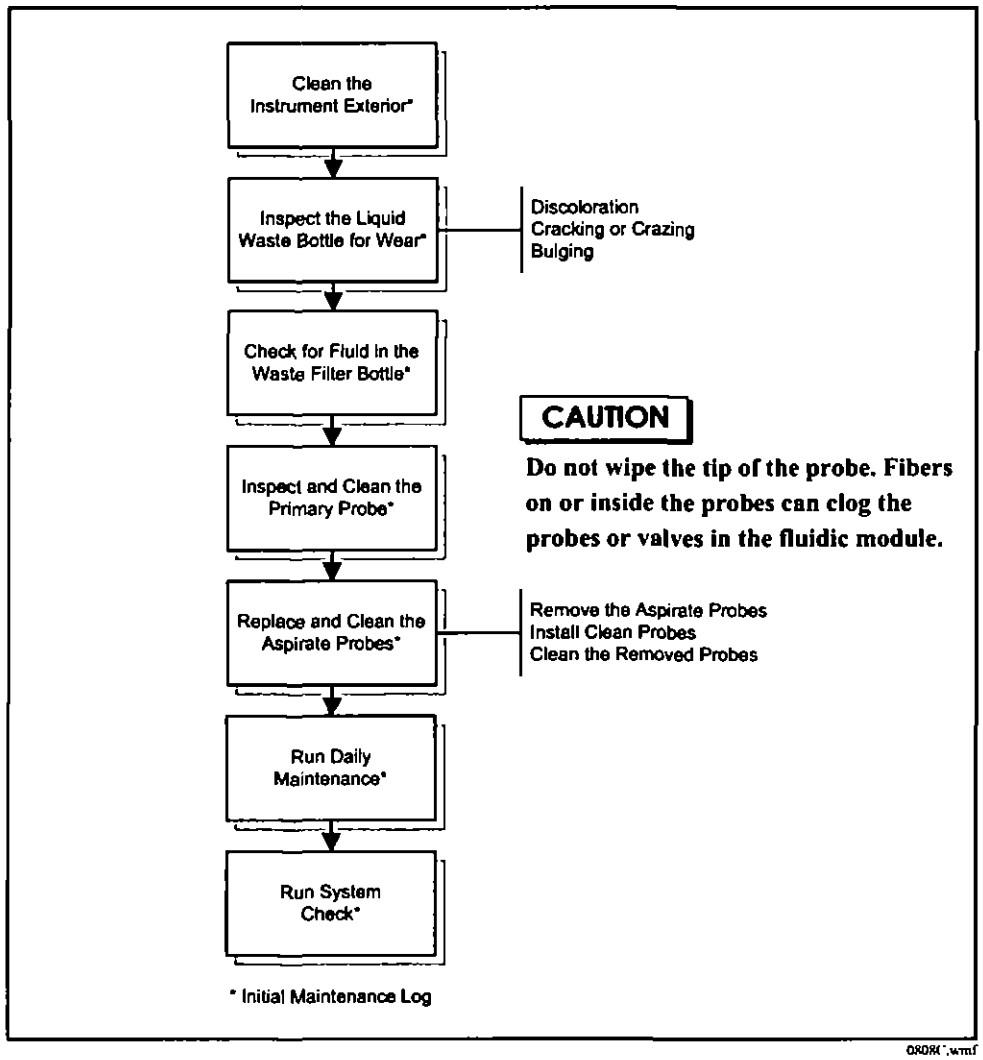
Weekly Maintenance Steps

WARNING

You will come in contact with potentially infectious materials during this procedure. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.



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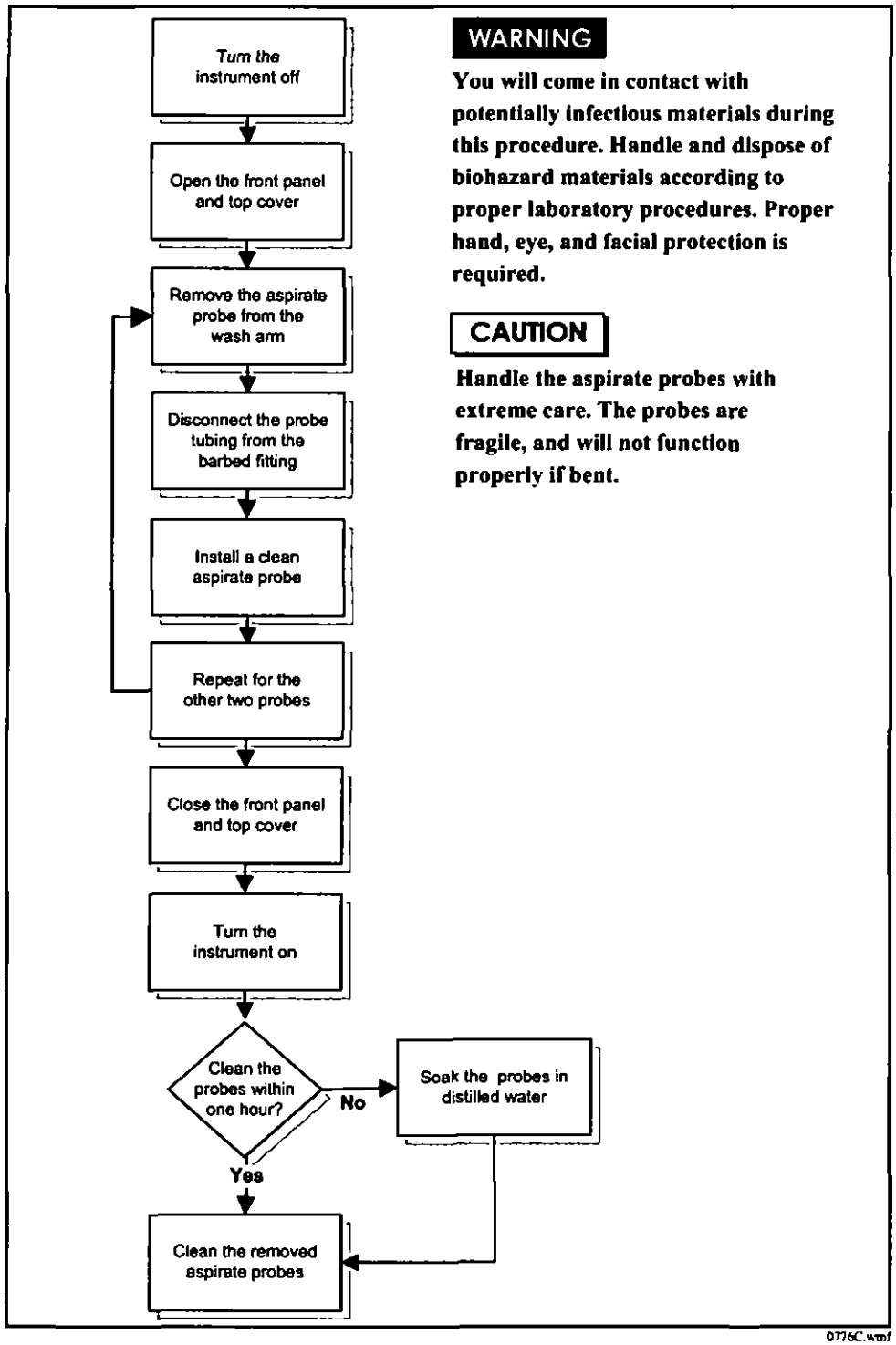
Replacing the Aspirate Probes



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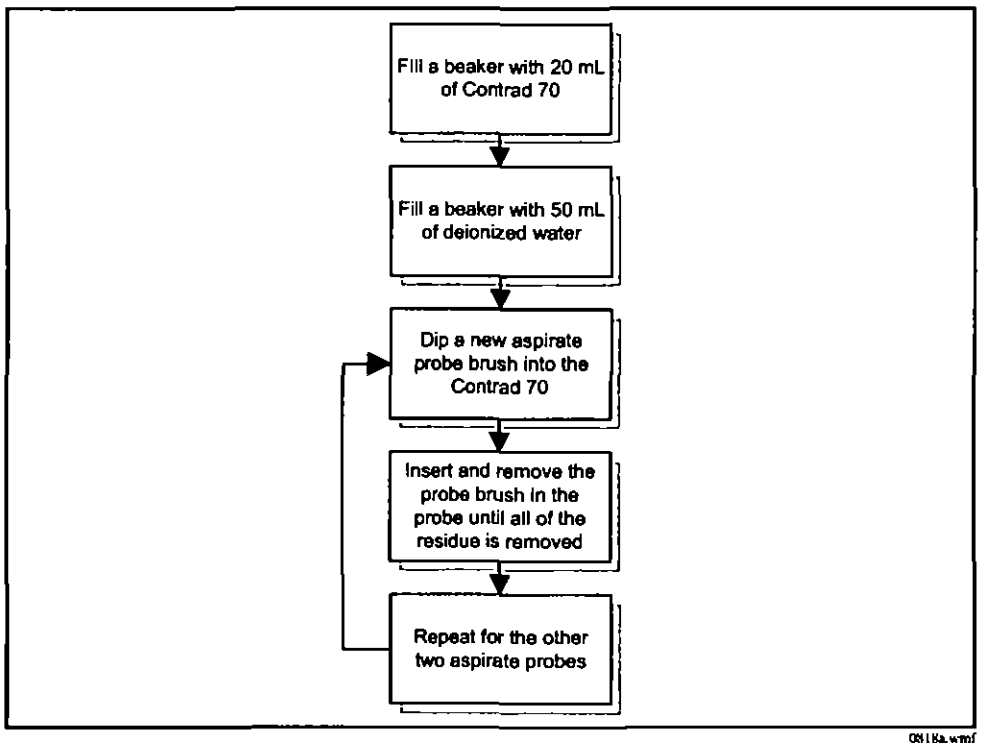
Precleaning the Aspirate Probes

WARNINGS

- **You will come in contact with potentially infectious materials during these procedures. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **Contrad 70 cleaning solution is alkaline and may cause severe eye irritation or mild skin irritation. See the manufacturer's label for details.**
- **Take the necessary precautions when removing and reinserting the probe brush to avoid scattering droplets of biohazardous material into the air.**
- **Once a disposable aspirate probe brush has been used to clean 1 to 3 aspirate probes, it is considered a biohazard. Handle and dispose of the brush according to appropriate laboratory safety procedures. Do not save a used brush for future use.**

CAUTIONS

- **Handle the aspirate probes with extreme care. The probes are fragile, and will not function properly if bent.**
- **The disposable aspirate probe brush handle bends easily.**



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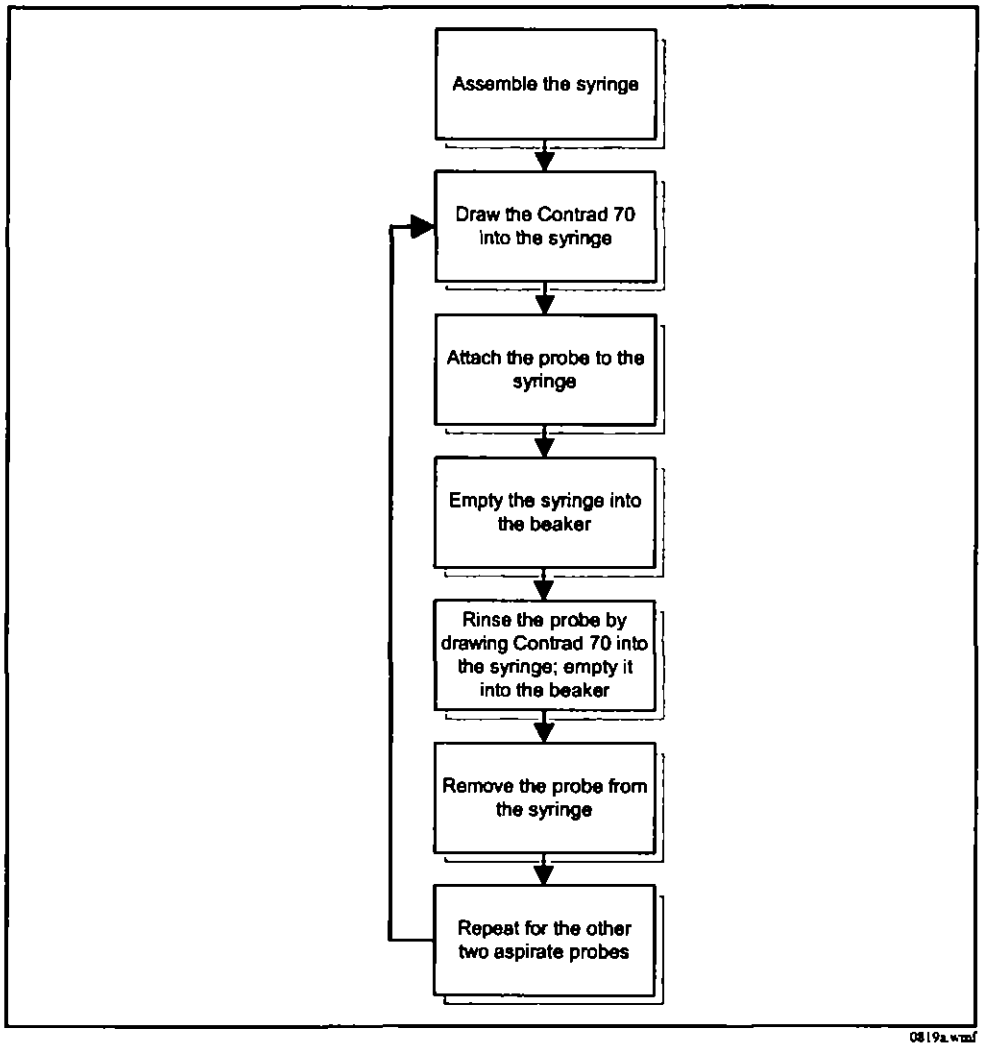
Cleaning the Aspirate Probes with Contrad 70 Cleaning Solution

WARNINGS

- **You will come in contact with potentially infectious materials during these procedures. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.**
- **Contrad 70 cleaning solution is alkaline and may cause severe eye irritation or mild skin irritation. See the manufacturer's label for details.**

CAUTIONS

- **Do not wipe the tip of the probe. Fibers on or inside the probes can clog the probes or valves in the fluidic module.**
- **Handle the aspirate probes with extreme care. The probes are fragile, and will not function properly if bent.**



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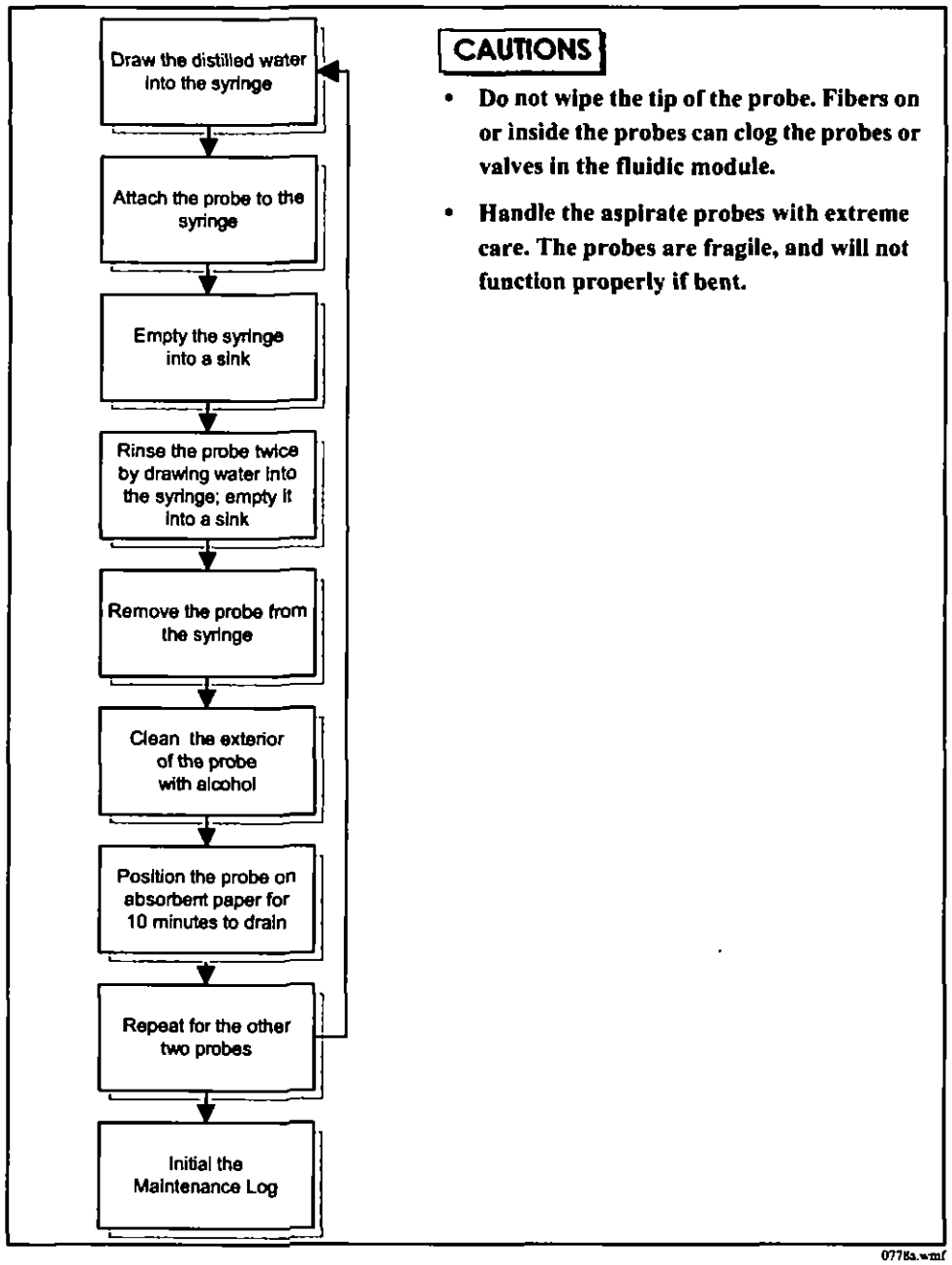
Cleaning the Aspirate Probes with Distilled Water

WARNING

You will come in contact with potentially infectious materials during these procedures. Handle and dispose of biohazard materials according to proper laboratory procedures. Proper hand, eye, and facial protection is required.



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System Check

You perform the System Check routine as part of weekly maintenance to verify system performance. During weekly maintenance, the three System Checks (washed, unwashed, and substrate) are run together. You can also run the System Check routine more often, or perform individual checks.

WARNINGS

- **Unless there is an emergency, let the System Check routine run to completion. Cancelling the routine may damage the instrument and compromise the integrity of subsequent test results.**
- **If you cancel the routine, do not initialize the system. Contact Technical Support for assistance.**
- **System Check Solution and wash buffer contain ProClin 300 preservative, which may cause sensitization by skin contact. After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.**

Required Materials

- 13 mm rack for 2 mL sample cups; the rack must have a rack ID between 1-57 or 400-456
- 2.0 mL sample cups (four cups)

NOTE

Use only the 2.0 mL sample cups when performing the maintenance routines. Using any other sample containers may result in level sensing errors and cancellation of the maintenance routine.

- Undiluted System Check Solution
- Wash buffer
- 1/501 dilution of System Check Solution (mix 20 µL System Check Solution with 10.0 mL Wash Buffer)
- Maintenance Log

System Check Expected Results

Compare the obtained results with the expected results. Expected results are listed in the Maintenance Log, included in this section.

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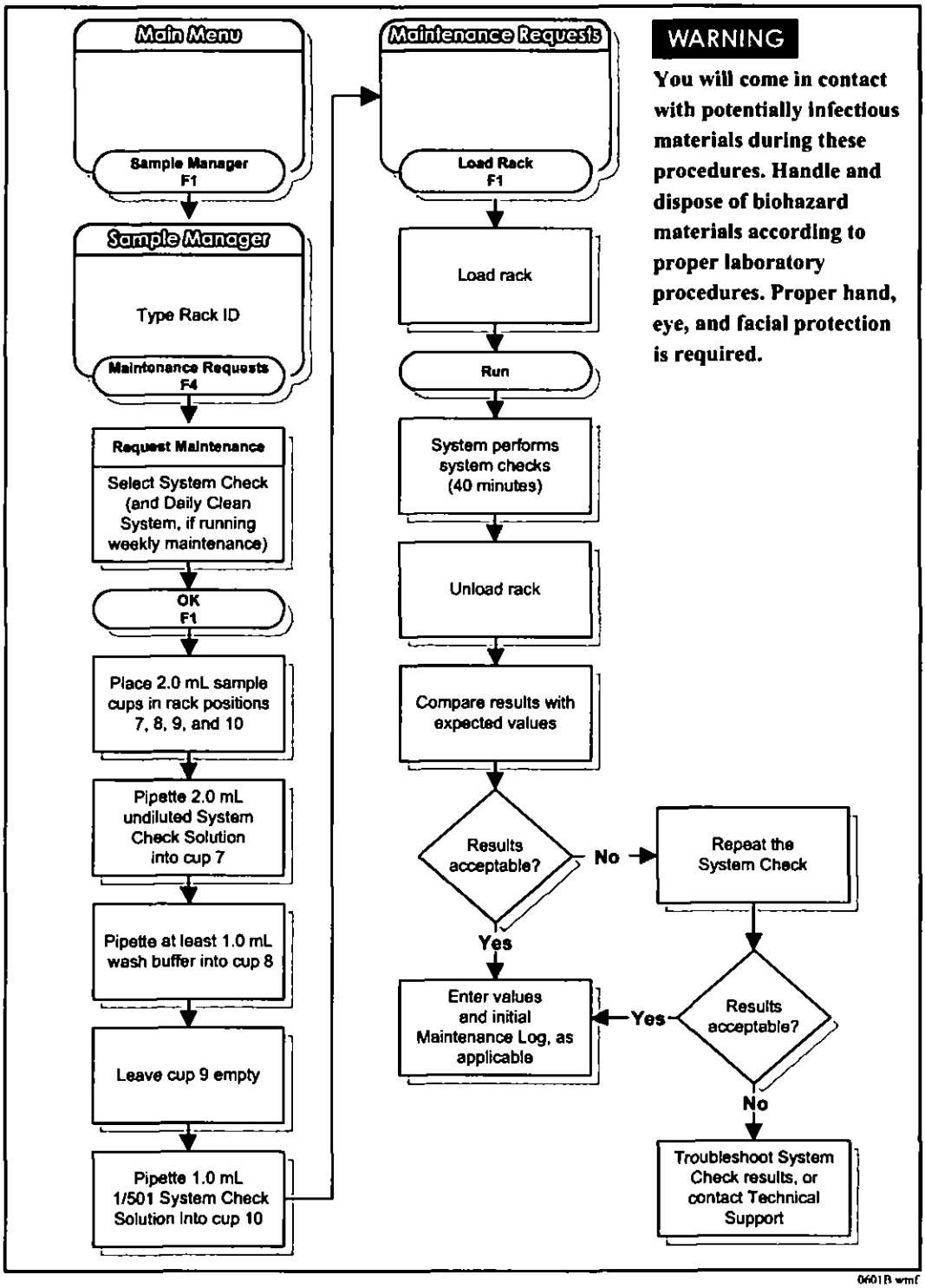
System Check Steps



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Access 2 Maintenance Log

Serial # _____ System ID _____ Month _____ Year _____ **Beckman Coulter, Inc.**

Perform the tasks listed at the left and draw a check (✓) in the accompanying box on the right. Initial the Tech Initials box.

DAILY MAINTENANCE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Check Zone Temperatures																															
Check System Supplies																															
Empty Liquid Waste Container																															
System Backup Successful?																															
Inspect Fluidic Module																															
Clean Probe Exteriors																															
Prime Substrate																															
Run Daily Clean System																															
(If Necessary) Perform Special Clean																															
Tech Initials																															

Perform the tasks listed at the left and draw a check (✓) in the accompanying box on the right. Initial the Tech Initials box.

WEEKLY MAINTENANCE	Week 1	Week 2	Week 3	Week 4	Week 5
Today's Date					
Clean Instrument Exterior					
Inspect Liquid Waste Bottle					
Check Waste Filter Bottle					
Inspect/Clean Primary Probe					
Replace/Clean Aspirate Probes					
Run Daily Maintenance	(Initial above)	(Initial above)	(Initial above)	(Initial above)	(Initial above)
Run System Check					
Tech Initials					

Enter the System Check Results in the boxes. Initial the Tech Initials box.

SYSTEM CHECK RESULTS	Week 1	Week 2	Week 3	Week 4	Week 5
Today's Date					
Washed RLU/%CV					
Substrate RLU/%CV					
Unwashed RLU/%CV					
Wash Efficiency PPM					
Substrate Ratio					
Substrate : Washed Ratio					
Tech Initials					

System Check Expected Results	
Washed Check	
RLU mean	5,000 to 20,000
%CV	≤ 12.00
Substrate Check	
RLU mean	5,000 to 9,000
%CV	≤ 5.00
Substrate ratio	0 to 1.40
Substrate : Washed Ratio	0 to 1.25*
Unwashed Check	
RLU mean	4 to 10 million*
%CV	≤ 2.00
Wash Efficiency	
PPM	-1.0 to +1.0

* The Substrate : Washed Ratio and the Unwashed Check RLU mean result are not system specifications. They are only reference guidelines.

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7 Troubleshooting

Event Log

The Event Log is a list of events the Access 2 system generates as it monitors the status of various system parameters. You can use these events to keep informed of system operations and to assist with troubleshooting.

NOTE

If you have a workgroup with more than one instrument, you can view only the events that are specific for the instrument attached to the PC displaying the Event Log.

Troubleshooting Events

If a system error or potential problem generates an event in the Event Log, you can view troubleshooting information for the event. This troubleshooting information includes:

- Possible causes for the event.
- Brief outline of troubleshooting instructions.
- Links to detailed procedures. Always review the detailed procedures if you are not completely familiar with them.

NOTE

Event troubleshooting information is available online within the Access 2 *Help* system.

You can view technical information about an event in the Details window. The event details, particularly the event code, can be useful for troubleshooting. If you contact Technical Support for assistance, the representative may request the details for one or more events.

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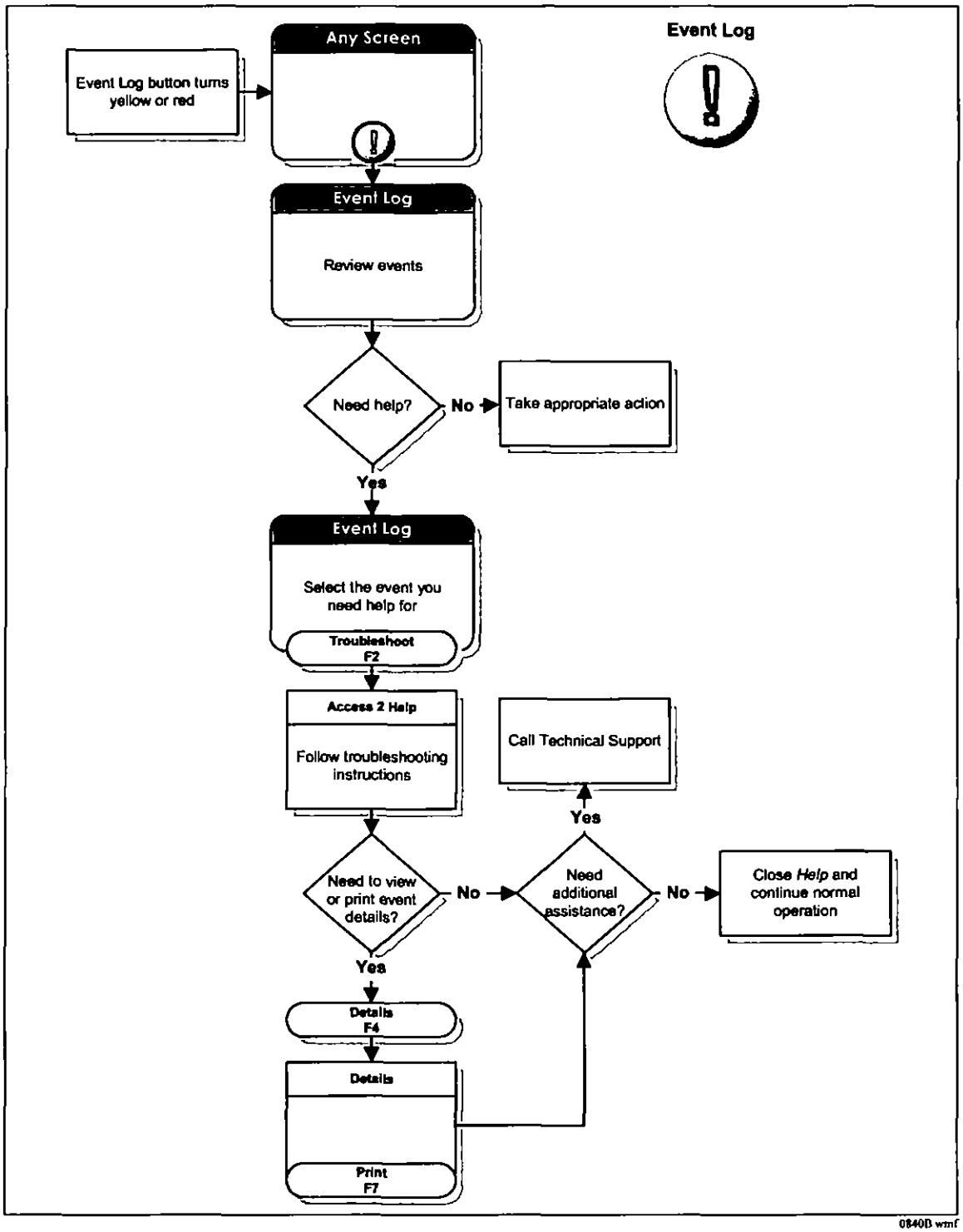
Troubleshooting Events



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System Check Troubleshooting

The System Check routine is typically run as part of weekly maintenance to verify that the Access 2 system is operating properly. It may also be run to troubleshoot another problem with the system or to verify proper operation after unscheduled maintenance is performed.

NOTE

The corrective actions in the troubleshooting tables contain abbreviated procedures. Regardless of the frequency with which you perform a procedure, regularly review the complete procedures, including their cautions for protecting the instrument from damage, and their warnings for ensuring your personal safety. Links to the procedures are available for the tables in the *Help* system.

Substrate Check Problems

If the System Check results are not within the expected ranges, troubleshoot the substrate check first. You should start here because problems with the substrate system can directly affect the unwashed and washed checks, and because the substrate check uses the fewest system components. When the substrate check results are within the expected ranges, the substrate and substrate system can be ruled out as the cause of the problem you are troubleshooting.

Substrate Check Troubleshooting

Symptoms	Possible Causes	Corrective Action
High %CV throughout the run	Insufficient supply of substrate	1. Check the level of substrate in the bottle. 2. If necessary, change the substrate bottle from the Supplies screen. 3. Repeat the System Check routine.
	Air in the substrate lines	1. Open the front panel. 2. Visually inspect the tubing at the substrate pump and heater for air bubbles. 3. If air bubbles are present: • Check the substrate pump and heater fittings, and the fitting on top of the substrate bottle. Finger-tighten any loose connections. Be careful not to overtighten any of the fitting connections. • Close the front panel and prime the substrate system for 4 cycles. 4. Open the front panel and inspect the tubing again. • If the bubbles are gone, close the front panel and repeat the System Check routine. • If you still see bubbles, contact Technical Support for further instructions.

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Substrate Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
High %CV throughout the run *(continued)*	Leak in the substrate system tubing	1. With the front panel open, open the top cover. 2. Visually inspect the tubing leading to and away from the substrate pump/valve/heater assembly for leaks and/or crystalline deposits. 3. Deposits may indicate the tubing is damaged and should be replaced. • If you find deposits, contact Technical Support for further instructions. • If you find no deposits, continue troubleshooting other possible causes.
	Kinked substrate system tubing	1. With the front panel and top cover open, visually inspect the tubing leading to and away from the substrate pump/valve/heater assembly for kinks. • If no kinks are found, continue troubleshooting other possible causes. 2. Straighten any kinks. Close the top cover and front panel. • If the kinked tubing is part of the substrate probe, remove and replace the substrate probe. 3. Close the top cover and front panel. 4. If you straightened kinks, but did not need to replace the substrate probe: • Prime the substrate system for 4 cycles. • Repeat the System Check routine.
	Bent substrate probe tip	1. With the front panel open, inspect the substrate probe tip. • If the substrate probe tip is not bent, continue troubleshooting other possible causes. 2. If the substrate probe tip is bent, remove and replace the substrate probe.
	Substrate pump or valve failure	Contact Technical Support.
	Luminometer problem	Contact Technical Support.
High %CV from high values in the last one or two replicates	System Check solution diluted incorrectly	1. Prepare a new 1/501 dilution using a new vial of System Check solution. 2. Repeat the System Check routine.
	Sample containers out of order in the maintenance rack	1. Place the sample containers in the correct order. 2. Repeat the System Check routine.
High RLU mean	Wash/read carousel or substrate temperatures too high (results may be flagged TRS or TRW)	1. Check the wash carousel and substrate temperatures on the Maintenance Review screen. 2. If the temperatures for either device is displayed in red (out of range), contact Technical Support.
	System Check solution diluted incorrectly	1. Prepare a new 1/501 dilution using a new vial of System Check solution. 2. Repeat the System Check routine.
	Sample containers out of order in the maintenance rack	1. Place the sample containers in the correct order. 2. Repeat the System Check routine.

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Substrate Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
High RLU mean ***(continued)***	Substrate pump delivering too much substrate	Run the Visual Substrate Volume Check procedure. • If the results do not fail, continue troubleshooting other possible causes. • If the results fail, contact Technical Support.
	Contaminated substrate supply	1. Contact Technical Support to verify the need to decontaminate the substrate system. 2. If Technical Support agrees, decontaminate the substrate system and then verify system performance.
	Luminometer problem	Contact Technical Support.
Low RLU mean	Expired substrate	1. Review the expiration date on the Supplies screen. 2. If necessary, change the substrate bottle from the Supplies screen. 3. Repeat the System Check routine.
	Improperly stored substrate (bottle stored at room temperature for too long)	1. Check the date the bottle was placed at room temperature. 2. If necessary, change the substrate bottle from the Supplies screen. 3. Repeat the System Check routine.
	Insufficient supply of substrate	1. Check the level of substrate in the bottle. 2. If necessary, change the substrate bottle from the Supplies screen. 3. Repeat the System Check routine.
	Wash/read carousel or substrate temperatures too low (results may be flagged TRS or TRW)	1. Check the wash carousel and substrate temperatures on the Maintenance Review screen. 2. If the temperatures for either device are displayed in red (out of range), contact Technical Support.
	Incomplete priming of the substrate after substrate system decontamination	1. Prime the substrate system for 20 cycles again. 2. Repeat the System Check routine.
	Substrate bottle contaminated with Citranox cleaning solution during substrate system decontamination	1. Change the substrate bottle from the Supplies screen. Do not prime the substrate system when prompted as you change the bottle. 2. Prime the substrate system from the Prime Fluidics window for 20 cycles. 3. Repeat the System Check routine.
	Substrate dispense volume too low	Run the Visual Substrate Volume Check procedure. • If the results do not fail, continue troubleshooting other possible causes. • If the results fail, contact Technical Support.
	Luminometer problem	Contact Technical Support.

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Substrate Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
No RLU values	Substrate bottle contaminated with Citranox cleaning solution during substrate system decontamination	1. Change the substrate bottle from the Supplies screen. Do not prime the substrate system when prompted as you change the bottle. 2. Prime the substrate system from the Prime Fluidics window for 20 cycles. 3. Repeat the System Check routine.
	Luminometer problem	Contact Technical Support.
RLUs trending up or down over time	Substrate delivery inconsistent	Troubleshoot according to the High %CV symptoms for substrate check.
	Substrate bottle contaminated with Citranox cleaning solution during substrate system decontamination	1. Change the substrate bottle from the Supplies screen. Do not prime the substrate system when prompted as you change the bottle. 2. Prime the substrate system from the Prime Fluidics window for 20 cycles. 3. Repeat the System Check routine.
High substrate ratio	Dirty or plugged aspirate probes	1. Clean the aspirate probes. 2. Repeat the System Check routine.
	Fluid dripping from aspirate probes	1. Open the front panel. 2. Visually inspect the tubing and the area under the tubing, from the peristaltic waste pump to the aspirate probes for leaks and/or crystalline deposits. 3. Deposits may indicate that the tubing is damaged and should be replaced. • If you find deposits, contact Technical Support for further assistance. • If you find no leaks/deposits, continue troubleshooting other possible causes.
	Plugged waste air filter	1. Check the tubing from the liquid waste bottle for constrictions. • If the tubing is constricted, clear it and repeat the System Check routine. 2. If the results fail, remove the tubing from the waste filter at the quick disconnect and place the end of the tubing in one of the adjacent holes. This may temporarily resolve the error until you can install a new waste filter assembly. 3. Repeat the System Check routine. • If the results are acceptable, contact Technical Support for assistance in ordering and replacing the waste filter assembly. • If the results fail, contact Technical Support.

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Unwashed Check Problems

Begin troubleshooting the unwashed check once you have determined that the substrate check results are within the expected ranges. The unwashed check troubleshooting table provides information about the pipetting system, and does not provide detail on problems related to the substrate or washing systems.

Unwashed Check Troubleshooting

Symptoms	Possible Causes	Corrective Action
High %CV	Air in the main pipettor fluid lines	1. Open the front panel. 2. Visually inspect the main pipettor line for air bubbles. Be sure to check the tubing leading out of the precision pump and entering the main pipettor. 3. If bubbles are present, prime the pipettor. 4. Inspect the tubing again. • If the bubbles are gone, run the System Check routine. • If you still see bubbles, contact Technical Support for further instructions.
	Wash buffer supply lines kinked	1. Open the front panel. 2. Visually inspect the tubing from the wash buffer supply to the main pipettor for kinks. • If no kinks are found, continue troubleshooting other possible causes. 3. Straighten any kinks and close the front panel. 4. Prime the pipettor. 5. Repeat the System Check routine.
	No wash buffer	1. Check the wash buffer supply in the fluids tray. • If the wash buffer reservoir is empty, but the **Wash Buffer** status button is not red, contact Technical Support. 2. If necessary, change the wash buffer bottle. 3. Repeat the System Check routine.
	Precision pump, valve, fittings, or tubing damaged and leaking	1. Open the front panel and the top cover. 2. Visually inspect the tubing leading from the precision pump valve, to the pressure monitor if applicable, to the main pipettor for leaks and/or crystalline deposits. 3. Examine the precision pump and valve for leaks and/or crystalline deposits. 4. Deposits may indicate that the pipetting system is damaged and should be replaced. • If you see deposits, contact Technical Support for further assistance. • If you do not see deposits, continue troubleshooting other possible causes.
	Worn or damaged precision pump seals	Contact Technical Support.

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Unwashed Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
High %CV *(continued)*	Problems with the substrate system: • Insufficient supply of substrate • Air in the substrate lines • Leak in the substrate system tubing • Kinked substrate system tubing • Bent substrate probe • Substrate pump or valve failure	1. If the substrate check %CV result is within the expected range, the substrate system is not the cause of the high %CV for the unwashed check. Continue troubleshooting other possible causes. 2. If the substrate check result is not within the expected range, troubleshoot the substrate check result.
	Primary probe partially plugged	1. Look at the Pressure Monitor screen to determine if a pressure sensor is present, and that obstruction detection is enabled. • If the pressure sensor is not present, or if it is present but obstruction detection is disabled, continue with step 2. • If obstruction detection is enabled, review the Event Log, and troubleshoot according to the events related to main pipettor obstructions or abnormal pressures. 2. Run the Special Clean routine. 3. Run the System Check routine. 4. If the results fail, contact Technical Support to verify the need to replace the primary probe. 5. When needed, remove and replace the primary probe.
	Splashing in the RVs	Contact Technical Support.
	Luminometer problem	Contact Technical Support.
High RLU mean	System Check solution diluted incorrectly	1. Prepare a new 1/501 dilution using a new vial of System Check solution. 2. Repeat the System Check routine.
	Sample containers out of order in the maintenance rack	1. Place the sample containers in the correct order. 2. Repeat the System Check routine.
	Problems with the substrate system: • Wash/read carousel or substrate temperatures too high • Contaminated substrate supply • Substrate pump delivering too much substrate	1. If the substrate check mean RLU result is within the expected range, the substrate system is not the cause of the high mean RLU result for the unwashed check. Continue troubleshooting other possible causes. 2. If the substrate check result is not within the expected range, troubleshoot the substrate check result.
	Luminometer problem	Contact Technical Support.
Low RLU mean	System Check solution diluted incorrectly	1. Prepare a new 1/501 dilution using a new vial of System Check solution. 2. Repeat the System Check routine.
	Sample containers out of order in the maintenance rack	1. Place the sample containers in the correct order. 2. Repeat the System Check routine.
	System Check expired or stored incorrectly	1. Prepare a new 1/501 dilution using a new vial of unexpired System Check solution. 2. Repeat the System Check routine.

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Unwashed Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Low RLU mean ***(continued)***	Problems with the substrate system: • Expired substrate • Insufficient supply of substrate • Wash/read carousel or substrate temperatures too low • Incomplete priming after substrate system decontamination • Substrate supply contaminated with Citranox cleaning solution during substrate system decontamination • Substrate dispense volume too low	1. If the substrate check RLU mean result is within the expected range, the substrate system is not the cause of the low RLU mean result for the unwashed check. Continue troubleshooting other possible causes. 2. If the substrate check result is not within the expected range, troubleshoot the substrate check result.
	Luminometer problem	Contact Technical Support.
Low RLU outliers	Ultrasonic transducer problem	Contact Technical Support.

Washed Check Problems

Begin troubleshooting the washed check once you have determined that the substrate check and unwashed check results are within the expected ranges. The washed check troubleshooting table provides information about the reaction vessel (RV) wash system, and does not provide detail on problems related to the substrate or the pipetting systems.

Washed Check Troubleshooting

Symptoms	Possible Causes	Corrective Action
High %CV	Dirty or plugged aspirate probes	1. Clean the aspirate probes. 2. Repeat the System Check routine.
	Damaged aspirate probes	1. Open the front panel. 2. Visually inspect the aspirate probes on the wash arm. 3. Replace any probes that are damaged. 4. With the front panel closed, repeat the System Check routine. 5. If the problem persists, contact Technical Support.
	Plugged waste air filter	1. Check the tubing from the liquid waste bottle for constrictions. • If the tubing is constricted, clear it and repeat the System Check routine. 2. If the results fail, remove the tubing from the waste filter at the quick disconnect and place the end of the tubing in one of the adjacent holes. This may temporarily resolve the error until you can install a new waste filter assembly. 3. Repeat the System Check routine. • If the results are acceptable, order a new waste filter assembly and replace the current one. • If the results fail, contact Technical Support.

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Washed Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
High %CV ***(continued)***	Damaged peristaltic waste pump tubing	1. Open the front panel and top cover. 2. Visually inspect the tubing and area under the tubing, from the peristaltic waste pump to the aspirate probes for leaks and/or crystalline deposits. 3. Deposits may indicate that the tubing is damaged and should be replaced. • If you see deposits, contact Technical Support for further assistance. • If you do not see deposits, continue troubleshooting other possible causes.
	One or more aspirate probes stuck in the "up" position	1. With the front panel open, verify that the aspirate probes can move up and down. • Grasp each probe gently just below the wash arm. • The probe should move up and down slightly. 2. Replace any probe that does not move freely. 3. With the front panel closed, repeat the System Check routine. 4. If the problem persists, contact Technical Support.
	Air in the wash pump system tubing	1. With the front panel open, visually inspect the tubing from the wash buffer supply to the dispense probes for air bubbles. 2. If you see bubbles, close the front panel and prime the dispense probes for 4 cycles. 3. Open the front panel and inspect the tubing again. • If the bubbles are gone, close the front panel and repeat the System Check routine. • If you still see bubbles, contact Technical Support for further instructions.
	Kinked wash pump system tubing	1. With the front panel open, visually inspect the tubing from the wash buffer supply to the dispense probes for kinks. • If no kinks are found, continue troubleshooting other possible causes. 2. Straighten any kinks. 3. Close the front panel and prime the dispense probes for 4 cycles. 4. Repeat the System check routine.
	Problems with the substrate system: • Insufficient supply of substrate • Air in substrate lines • Leak in the substrate system tubing • Kinked substrate system tubing • Bent substrate probe • Substrate pump or valve failure	1. If the substrate check %CV result is within the expected range, the substrate system is not the cause of the high %CVs for the washed check. Continue troubleshooting other symptoms. 2. If the substrate check result is not within the expected range, troubleshoot the substrate check result.

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Washed Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
High %CV ***(continued)***	Problems with the pipetting system: • No wash buffer • Worn or damaged precision pump seals • Partially plugged primary probe • Precision pump, valve, fittings, or tubing damaged and leaking	1. If the unwashed check %CV result is within the expected range, the pipetting system is not the cause of the high %CV for the washed check. Continue troubleshooting other possible causes. 2. If the unwashed check result is not within the expected range, troubleshoot the unwashed check result.
	Incorrect aspirate probe height	Contact Technical Support.
	Defective peristaltic waste pump	Contact Technical Support.
	RV mixing problem	Contact Technical Support.
	Splashing in the RVs	Contact Technical Support.
High RLU mean	Dirty or plugged aspirate probes	1. Clean the aspirate probes. 2. Repeat the System Check routine.
	Damaged aspirate probes	1. Open the front panel. 2. Visually inspect the aspirate probes on the wash arm. 3. Replace any probes that are damaged. 4. With the front panel closed, repeat the System Check routine. 5. If the problem persists, contact Technical Support.
	One or more aspirate probes stuck in the "up" position	1. With the front panel open, verify that the aspirate probes can move up and down. • Grasp each probe gently just below the wash arm. • The probe should move up and down slightly. 2. Replace any probe that does not move freely. 3. With the front panel closed, repeat the System Check routine. 4. If the problem persists, contact Technical Support.
	Problems with the substrate system: • Wash/read carousel or substrate temperatures too high • Contaminated substrate supply • Substrate pump delivering too much substrate	1. If the substrate check RLU mean result is within the expected range, the substrate system is not the cause of the high RLU mean result for the unwashed check. Continue troubleshooting other possible causes. 2. If the substrate check result is not within the expected range, troubleshoot the substrate check result.
	Incorrect aspirate probe height	Contact Technical Support.
	Luminometer problem	Contact Technical Support.

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Washed Check Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Low RLU mean	Diluted System Check solution used instead of undiluted	1. Be sure that sample container 1 contains undiluted System Check solution. 2. Repeat the System Check routine.
	Containers 1 and 4 switched in the maintenance rack	1. Be sure that sample container 1 contains undiluted System Check solution and sample container 4 contains 1/501 diluted System Check. 2. Repeat the System Check routine.
	Problems with the pipetting system	1. If the unwashed check %CV result is within the expected range, the main pipettor is not the cause of the low RLU mean result for the washed check. Continue troubleshooting other possible causes. 2. If the unwashed check result is not within the expected range, troubleshoot the unwashed check result.
	Problems with the substrate system: • Air in the substrate lines • Leak in the substrate system tubing • Kinked substrate system tubing • Bent substrate probe • Substrate pump or valve failure • Expired substrate • Insufficient supply of substrate • Wash/read carousel or substrate temperatures too low • Incomplete priming after substrate system decontamination • Substrate supply contaminated with Citranox cleaning solution during substrate system decontamination • Substrate dispense volume too low	1. If the substrate check %CV and RLU mean results are within expected ranges, the substrate system is not the cause of the low RLU mean result for the washed check. Continue troubleshooting other possible causes. 2. If the substrate check results are not within the expected ranges, troubleshoot the substrate check result.
	Luminometer problem	Contact Technical Support.

Wash Efficiency Problems

The wash efficiency is a calculation based upon the results from the substrate, washed, and unwashed checks of the System Check routine. The wash efficiency value provides information about the washing system.

Wash Efficiency Troubleshooting

Symptoms	Possible Causes	Corrective Action
Wash Efficiency PPM fails to meet criteria	Problems with the RV wash system (washed check mean RLUs or %CVs too high)	Troubleshoot the washed check result.
	Problems with the pipetting system (unwashed check mean RLUs too low)	Troubleshoot the unwashed check result.
	Problems with the substrate system (contaminated substrate bottle)	Troubleshoot the substrate check result.

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Instrument Troubleshooting

Instrument troubleshooting information can help you identify and correct instrument problems that are not resolved during System Check troubleshooting. Most instrument troubleshooting is available through the Event Log. The information in this section addresses problems you notice during operation or inspection that do not generate a caution or warning event.

NOTE

The corrective actions in the troubleshooting tables contain abbreviated procedures. Regardless of the frequency with which you perform a procedure, regularly review the complete procedures, including their cautions for protecting the instrument from damage, and their warnings for ensuring your personal safety. Links to these procedures are available for these tables in the *Help* system.

General Instrument Problems

General Instrument Troubleshooting

Symptoms	Possible Causes	Corrective Action
System mode is Not Ready	System rebooting or initializing	Wait for the instrument to finish rebooting or initializing. When this occurs, the system mode will change to the **Ready** mode and any text message in the system mode area will disappear.
	Many circumstances other than rebooting or initializing can place the instrument in the **Not Ready** mode, some examples are: • Front panel of the instrument is open • Pipettor gantry was just cleaned • System detected a device motion error • **Stop** was selected during a maintenance routine	**Warning:** **If the system is in the Not Ready mode because Stop was selected during a maintenance routine, do not initialize the system. Contact Technical Support for assistance.** The system must be initialized to return to the **Ready** mode. • If you are experienced at initializing the system, and are following instructions in *Help* or in an Access 2 manual, initialize the system. • If you are not experienced at initializing the system or you are not following instructions in *Help* or in an Access 2 manual, contact Technical Support.
The Event Log button is yellow or red	System event occurred	Review the event log message and its troubleshooting information. Take the recommended corrective action.
System performance is slow	Database contains too many test and QC results	1. Set up the system to automatically delete test and QC results from the database. 2. If the Auto-Delete function is already set up, consider reducing the number of days that must elapse before the test results are deleted.

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Instrument Start-Up Problems

Use the following table to troubleshoot the instrument if you are having problems rebooting or initializing the Access 2 system and no events report in the Event Log. If an event is generated, follow the Event Log troubleshooting procedures.

Instrument Start-Up Troubleshooting

Symptoms	Possible Causes	Corrective Action
System fails during reboot	No power to instrument	Refer to the power supply troubleshooting table.
	CD in CD-ROM or DVD drive, or data disk in 3.5-inch disk drive.	Remove the CD from the CD-ROM or DVD drive, or remove the disk from 3.5-inch disk drive and reboot the instrument.
	Instrument hardware (power supply, internal hard drive, CPU, printed circuit board) or software failure	Reboot the instrument.
System fails during initialization	Interlock switch detects front panel of instrument is open	Close the front panel of the instrument and initialize the system.

Power Supply Problems

Use the following table to troubleshoot when the instrument or the peripheral devices do not have power. The peripheral devices that require a power supply include the external computer (PC), touch screen monitor, and printer.

Power Supply Troubleshooting

Symptoms	Possible Causes	Corrective Action
No power to the instrument or peripherals	Faulty power outlet or power strip	1. Plug the instrument and the peripherals into a different power outlet or strip. 2. If the problem persists, troubleshoot the power system for the instrument and each peripheral device individually. 3. When the source of the problem has been identified, contact Technical Support if necessary.
No power to the instrument	Instrument power switch not on	Turn on the power switch located on the right side of the instrument.
	Power cord connector loose at either end	Be sure that the power cord connections to the outlet and instrument are plugged in tightly.
	Faulty power supply or circuit breaker	Contact Technical Support.
No power to peripheral(s)	Peripheral device power switch not on	1. Turn on the peripheral device power switch. 2. If you cannot locate the power switch, see the documentation provided by the manufacturer.
	Peripheral device power cord connector loose at either end	Be sure that the power cord connections to the outlet and peripheral device are plugged in tightly.
	Defective peripheral device	Contact Technical Support.

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Keyboard Problems

Use the following table to troubleshoot situations when the computer keyboard is not responding to your key strokes.

Keyboard Troubleshooting

Symptoms	Possible Causes	Corrective Action
No response from the keyboard	Loose connector	Be sure that the cable connections (located on the back side of the external computer) between the keyboard, the handheld bar code reader, and the computer are plugged in tightly.
	Invalid key selected	Look at the status line above the function buttons near the bottom of the screen to verify that the key selected is an acceptable keyboard response.
	System software not responding	Reboot the PC.
	Hardware problem	Contact Technical Support.

Printer Problems

Use the following table to troubleshoot problems with the printer.

Printer Troubleshooting

Symptoms	Possible Causes	Corrective Action
Print job was not printed, or is incomplete	Communication interrupted between system and printer	1. Check the printer paper tray. • If empty, load paper into the printer paper tray. 2. Try to print the missing or incomplete report once. • If print service is restored, continue normal operation. 3. If print service is not restored, reboot the PC. 4. If print service is not restored, locate missing report and print from the appropriate screen. For example, print a missing Calibration report from the Calibration screen. 5. If the report does not print, be sure the cable connections between the printer and the computer are plugged in tightly. 6. Reload paper into the printer paper tray. 7. Try to print the report again. 8. If report still does not print, contact Technical Support.

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Bar Code Reading Problems

Use the following table to troubleshoot when the bar code reader does not scan bar code information.

Bar Code Reader Troubleshooting

Symptoms	Possible Causes	Corrective Action
Sample rack bar code label was not read by the internal bar code reader	Bar code label attached incorrectly to the rack	Attach the bar code label correctly.
	Incorrect system bar code label on rack	If the sample rack is labeled with an Access (not an Access 2) system label, the rack cannot be used. Either replace the bar code label with an Access 2 rack label or move the samples to an Access 2 labeled rack.
	Bar code reader not operating properly	Contact Technical Support.
Sample bar code label was not read by the internal bar code reader	Sample bar code reading not enabled	Set up the bar code reader to read sample IDs.
	Sample container placed incorrectly in the rack	Turn the sample container until its bar code label faces the same direction as the rack bar code label, and is visible through the slot in the sample rack.
	Bar code label applied incorrectly on the sample container	Apply the bar code label correctly on the sample container.
	Bar code reader not set up to read the sample bar code symbology	Setup the bar code reader parameters to match the symbology you are using.
	Bar code symbology or parameters not supported	1. Verify that the bar code symbology and parameters used on the sample label are supported. 2. If the symbology or parameters are not supported, contact Technical Support.
	Number of bar code characters on label does not agree with the number of characters specified in the Bar Code Reader Setup window (for Interleaved 2 of 5 only)	1. Check the number of characters entered for the Interleaved 2 of 5 symbology in the Bar Code Reader Setup window. 2. If necessary, change the number of characters to match the number of characters on the label. 3. If the number of characters match, contact Technical Support.
No response from the handheld bar code reader	Incorrect scanning technique	1. Verify the following: • The correct screen or window is displayed for the item you are scanning. • The correct field is selected. 2. Scan the label a second time.
	Loose connector	Be sure that the cable connections (located on the back side of the external computer) between the keyboard, the handheld bar code reader, and the computer are plugged in tightly.
	System software not responding	Reboot the PC.
	Handheld bar code reader not configured properly	Contact Technical Support.
	Hardware problem	Contact Technical Support.

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Air in the System

Air bubbles in the fluid lines can lead to poor precision. If you notice air in the lines, use the following table to troubleshoot the problem.

Troubleshooting Air in the System

Symptoms	Possible Causes	Corrective Action
Air in the fluid lines	Insufficient priming	1. Prime all fluidic components. 2. Run the System Check routine. 3. If the problem persists, contact Technical Support.
	System prime lost due to a leak in the fluidic system	1. Be sure the connections between the fittings (located on the left side of the instrument) and the fluids tray fit together tightly. Visually inspect the tubing and fittings for leaks and deposits. 2. Visually inspect the fluidic module tubing and fittings for leaks and deposits. 3. Inspect the precision pump valve and valve fittings for leaks and deposits. 4. Leaks and deposits may indicate that the fluidics system is damaged. • If you find leaks and deposits, contact Technical Support for further assistance. • If you find no leaks or deposits, continue troubleshooting other possible causes.
	Kinked tubing in the fluids tray	1. Visually inspect all tubing leading away from the fluids tray components for kinks. Pay close attention to the tubing leading away from the substrate bottle. • If no kinks are found, continue troubleshooting other possible causes. 2. Straighten any kinks. 3. Prime all fluidic components. 4. Run the System Check routine.
	Plugged waste air filter	1. Check the tubing from the liquid waste bottle for constrictions. • If the tubing is constricted, clear it and repeat the System Check routine. 2. If the results fail, remove the tubing from the waste filter at the quick disconnect and place the end of the tubing in one of the adjacent holes. This may temporarily resolve the error until you can install a new waste filter assembly. 3. Repeat the System Check routine. • If the results are acceptable, order a new waste filter assembly and replace the current one. • If the results fail, contact Technical Support.

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Main Pipettor Problems

Problems with the main pipettor can lead to poor precision. If you notice any leaking or deposits, use the following table to troubleshoot the problem.

Main Pipettor Troubleshooting

Symptoms	Possible Causes	Corrective Action
Main pipettor leaking	Primary probe partially plugged	1. Look at the Pressure Monitor screen to determine if a pressure sensor is present, and that obstruction detection is enabled. • If the pressure sensor is not present, or if it is present but obstruction detection is disabled, continue with step 2. • If obstruction detection is enabled, review the Event Log, and troubleshoot according to the events related to main pipettor obstructions or abnormal pressures. 2. Run the Special Clean routine. 3. Run the System Check routine. 4. If the results fail, contact Technical Support to verify the need to replace the primary probe. 5. When needed, remove and replace the primary probe.
	Loose fitting between the main pipettor and precision pump valve	1. Open the front panel and top cover. 2. Visually inspect the fittings between the primary probe and precision pump valve for leaks and deposits. 3. Inspect all fluid fittings to the manifold for leaks and deposits. 4. Leaks or deposits may indicate that the tubing or fittings are damaged. • If you find leaks or deposits, contact Technical Support for further assistance. • If you find no leaks or deposits, continue troubleshooting other possible causes.
Main pipettor dispensing fluid with excess pressure	Primary probe partially plugged, causing the main pipettor to dispense fluid with too much pressure	1. Look at the Pressure Monitor screen to determine if a pressure sensor is present, and that obstruction detection is enabled. • If the pressure sensor is not present, or if it is present but obstruction detection is disabled, continue with step 2. • If obstruction detection is enabled, review the Event Log, and troubleshoot according to the events related to main pipettor obstructions or abnormal pressures. 2. Check RV locations 1 and 2 of the RV Shuttle for crystalline deposits. • If you find no deposits, continue troubleshooting other possible causes. 3. Run the Special Clean routine. 4. Run the System Check routine. 5. If the results fail, contact Technical Support to verify the need to replace the primary probe. 6. When needed, remove and replace the primary probe.

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Communication Problems

Use the following table to troubleshoot communication problems between the external computer (PC) and the instrument, or other systems in your workgroup.

Communications Troubleshooting

Symptoms	Possible Causes	Corrective Action
Communication between PC and instrument interrupted for more than 30 minutes during a run, PC locks up after communication is reestablished	Function that requires communication between the PC and the instrument, such as getting a rack or loading supplies, was attempted while the PC was updating the Test Results screen	Contact Technical Support.
Workgroup communication error occurs during rebooting process	Loose connection between PC and other systems in the workgroup	1. Be sure that the Access 2 instrument power switch is on. • If the power switch is off, restart the instrument. • If the power switch is on, but there is no power to the instrument, refer to the power supply troubleshooting table. 2. Check both ends of the cable connecting the PC to the other systems in your workgroup: • If the cable connection is loose at either end, connect it securely. • If the cable is not loose, contact Technical Support. 3. Reboot the PC.

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Assay Troubleshooting

Assay troubleshooting information provides troubleshooting tables to help you identify and correct assay-related problems. Before using assay troubleshooting information to troubleshoot assay issues, run the System Check routine and troubleshoot unexpected results. Running the System Check routine will help you to identify and correct, or rule out, some system issues as the cause of your problem.

NOTE

The corrective actions in the troubleshooting tables contain abbreviated procedures. Regardless of the frequency with which you perform a procedure, regularly review the complete procedures, including their cautions for protecting the instrument from damage, and their warnings for ensuring your personal safety. Links to these procedures are available for these tables in the *Help* system.

Assay Calibration Problems

When a calibration fails, the system displays a failure code in the reason field on the Calibration Data screens. Use the following table to help you troubleshoot the calibration problem.

Assay Calibration Troubleshooting

Symptoms	Possible Causes	Corrective Action
Although precision is good, the calibration fails for any reason other than Insuff Data	Multi-level calibrators pipetted out of order: • Calibration curve does not ascend or descend smoothly. • Calibration cutoff is opposite of the expected result.	1. Be sure that the calibrators are placed in the rack in the proper order. 2. Repeat the calibration.
	Expired calibrator	1. Check the expiration date on the calibrator vial(s) or the Calibrator Setup screen. 2. If the calibrator is expired, add a new, unexpired calibrator on the Calibrator Setup screen. 3. Repeat the calibration.
	Calibrator unstable or contaminated due to improper handling	Repeat the calibration. If possible, repeat with a new set of the same calibrator lot.
	Reagent pack unstable or contaminated due to improper handling	1. Unload the reagent pack and load a new reagent pack. • If the lot number of the new reagent pack is different than the removed pack, recalibrate the assay. 2. For calibration problems, repeat the calibration.
	Contaminated substrate supply	1. Contact Technical Support to verify the need to decontaminate the substrate system. 2. If Technical Support agrees, decontaminate the substrate system and then verify system performance.
	Incorrect calibration information entered during calibrator setup	1. Verify the calibration information on the Calibrator Setup screen. 2. If necessary, edit the information on the Calibrator Setup screen. 3. Repeat the calibration.

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Assay Calibration Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Although precision is good, the quantitative curve is flat or the qualitative result is No Value; calibration fails for any reason other than Insuff Data	Wrong calibrator placed in rack	1. Be sure that the correct calibrator is loaded on the rack. 2. Repeat the calibration.
	Wrong reagent pack loaded, or placed in an incorrect position on the reagent carousel	1. Verify that the reagent pack was loaded by checking the Supplies screen. If it is missing, load a reagent pack. 2. If the reagent pack is listed on the screen, verify its location by unloading it from the carousel. • If the reagent pack is on-board, but is not presented during this process, contact Technical Support for assistance. • If Technical Support confirms a misplaced reagent pack, retrieve the pack. 3. Reload the reagent pack after you have verified its location. 4. Repeat the calibration.
Poor precision, and calibration fails for any reason other than Insuff Data	Daily or weekly maintenance not performed	1. Perform daily or weekly maintenance. 2. Repeat the calibration.
	Problems with the pipetting system: • Air in the main pipettor fluid lines. • Wash buffer supply lines kinked. • Precision pump, valve, fittings, or tubing damaged and leaking.	1. If the System Check routine results are within the expected ranges, the pipetting system is not the cause of the calibration failure. Continue troubleshooting other possible causes. 2. If the unwashed check result is not within the expected range, troubleshoot the unwashed check result.
	Problems with the substrate system: • Insufficient supply of substrate. • Air in the substrate lines. • Kinked substrate system tubing. • Leak in the substrate system tubing.	1. If the System Check routine results are within the expected ranges, the substrate system is not the cause of the calibration failure. Continue troubleshooting other possible causes. 2. If the substrate check result is not within the expected range, troubleshoot the substrate check result.
	Reagent gone because it leaked out of the pack during off-board storage	1. Load a new reagent pack. 2. Repeat the calibration.
RLUs are too low at one end of the calibration curve, and calibration fails for any reason other than Insuff Data	Reagent pack switch occurred, and the second reagent pack is missing or loaded incorrectly (RLUs drop off suddenly at the end of the calibration curve)	1. Verify that the second reagent pack was loaded by checking the Supplies screen. If the pack is missing, load a new reagent pack. 2. If the second reagent pack is listed on the screen, verify its location by unloading it from the carousel. • If the reagent pack is on-board, but is not presented during this process, contact Technical Support for assistance. • If Technical Support confirms a misplaced reagent pack, retrieve the pack. 3. Reload the second pack after you have verified its location. 4. Repeat the calibration.

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Assay Calibration Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Calibration fails for the reason Insuff Data	Quantity of calibrator not sufficient for testing (QNS result flag and event)	1. Calculate the correct volume of calibrator needed for the number of replicates and type of sample container used. 2. Pipette the amount of calibrator calculated in step 1 into the appropriate sample container. 3. Be sure the rack and rack ID are correct. 4. Repeat the calibration. 5. If the calibration fails again, contact Technical Support for assistance.
	Two or more replicates not calculated due to instrument error	1. Review the Event Log messages for device errors prior to the calibration failure. 2. Review the Test Results screen for any error messages. 3. Troubleshoot the device errors. If necessary, contact Technical Support for assistance. 4. After resolving the device errors, repeat the calibration.
	Sample container missing or placed in incorrect position in the rack	1. Be sure that the sample containers are in the proper order in the rack. 2. Repeat the calibration.

Quality Control Problems

When a quality control result violates an applied QC rule, the **Quality Control** button turns red. The button remains red until you review the QC Data screen. Use the following table to help you troubleshoot problems with your QC results.

Quality Control Troubleshooting

Symptoms	Possible Causes	Corrective Action
Controls violate applied QC rule	Daily or weekly maintenance not performed	1. Perform daily or weekly maintenance. 2. Repeat the test(s).
	Wrong quality control loaded onto the sample rack	1. Load the correct QC control. 2. Repeat the test(s).
	Wrong quality control lot number selected for the test	Repeat the test(s) using the correct lot number.
	Wrong mean and/or standard deviation information entered when setting up the quality controls	1. Review the QC information using **Edit Control F2** from the QC Setup screen. 2. If necessary, edit the information. 3. Repeat the test(s).

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Quality Control Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Controls violate applied QC rule *(continued)*	Quality control sample type does not match QC setup	1. Verify that the sample type used matches what is listed on the Test Request screen. 2. Verify that the sample type used matches the sample type set up for the quality control. 3. If the quality control sample type entered during setup is incorrect, you must delete the control and set up the control again using the correct sample type.
	Expired quality control	Load new, unexpired quality control, and repeat the test(s).
	Quality controls unstable or contaminated due to incorrect handling	1. Prepare new quality controls according to the procedure provided by the manufacturer. 2. Load the freshly prepared quality controls and repeat the test(s).
	Quality controls reconstituted incorrectly	1. Reconstitute new quality controls according to the procedure provided by the manufacturer. 2. Load the freshly reconstituted quality controls and repeat the test(s).
	Quantity of quality control not sufficient for testing (QNS result flag and event)	1. Calculate the correct volume of quality control needed for the number of replicates and type of sample container used. 2. Pipette the amount of quality control calculated in step 1 into the appropriate sample container. 3. Be sure the rack and rack ID are correct. 4. Repeat the test(s). 5. If the test(s) fail again, contact Technical Support for assistance.
	Quality controls evaporating from being on the instrument too long	1. Load a fresh aliquot of each quality control. 2. Repeat the test(s). Be sure the controls are pipetted into the RVs within one hour of loading onto the instrument. Be sure controls from 3 mL sample containers are pipetted into the RVs within two hours of loading.
	Reagent pack unstable or contaminated due to improper handling	1. Unload the reagent pack and load a new reagent pack. • If the lot number of the new reagent pack is different than the expired pack, recalibrate the assay. 2. Repeat the test(s).

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Quality Control Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Controls violate applied QC rule *(continued)*	Wrong reagent pack loaded, or placed in an incorrect position on the reagent carousel	1. Verify that the reagent pack was loaded by checking the Supplies screen. If it is missing, load a reagent pack. 2. If the reagent pack is listed on the screen, verify its location by unloading it from the carousel. • If the reagent pack is on-board, but is not presented during this process, contact Technical Support for assistance. • If Technical Support confirms a misplaced reagent pack, retrieve the pack. 3. Reload the reagent pack after you have verified its location. 4. Repeat the test(s).
	Expired reagent pack	1. Check the reagent pack expiration date on the Reagent Inventory screen. 2. Unload the expired reagent pack and load a new one. • If the lot number of the new reagent pack is different than the expired pack, recalibrate the assay. 3. Repeat the test(s).
	Wrong sample container and/or rack	Load the samples using appropriate sample containers and racks. Be sure that the sample containers are in a rack with the correct rack ID.
	Sample container missing or placed in incorrect position in the rack	1. Be sure that the sample containers are in the proper order in the rack. 2. Repeat the test(s).
	Expired assay calibration	1. Check the **Reagent Pack** button on the Supplies screen. If the lot number is red, the calibration has expired. 2. View the test results. Any test results calculated with an expired calibration will be flagged. 3. Recalibrate the assay. 4. Repeat the test(s).
	Quality Controls (QC) not run after preventive maintenance or repair	1. Run QC. 2. Evaluate any out-of-range QC results according to your established laboratory procedures. 3. Troubleshoot any test result flags, and recalibrate the assay if necessary. 4. Repeat the test.
	Substrate not equilibrated to room temperature when loaded on the system	The substrate must be at room temperature for specified period of time before it is loaded. For more information about the substrate, refer to the reagent instructions for use.

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Quality Control Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Increasing values across the run	Quality controls evaporating from being on the instrument too long	1. Load a fresh aliquot of each quality control. 2. Repeat the test(s). Be sure the controls are pipetted into the RVs within one hour of loading onto the instrument. Be sure controls from 3 mL sample containers are pipetted into the RVs within two hours of loading.

Patient Sample Problems

Use the following table to troubleshoot problems with your patient sample test results. If a special circumstance exists for a test result, the Access 2 system will code the result with a flag. The flags are either fatal (no calculated result), or non-fatal (the result was calculated, but a condition exists for that result). You can use these flags to assist you in the troubleshooting process.

Patient Sample Troubleshooting

Symptoms	Possible Causes	Corrective Action
Unexpected sample results	Incorrect patient sample type	Refer to the reagent instructions for use for the appropriate sample types for each assay.
	Patient sample handled incorrectly	Be sure that sample is stored and handled according to proper laboratory procedures. Refer to individual assay reagent instructions for use for proper sample handling instructions.
	Microclots present in the serum sample	1. Spin the sample again or use a serum filter to separate the serum from any microclots. 2. Repeat the test(s).
	Quantity of patient sample not sufficient for testing (QNS result flag and event)	1. Calculate the correct volume of patient sample needed for the number of replicates and type of sample container used. 2. Pipette the amount of quality control calculated in step 1 into the appropriate sample container. 3. Be sure the rack and rack ID are correct. 4. Repeat the test(s). 5. If the test(s) fail again, contact Technical Support for assistance.
	Patient samples evaporating from being on the instrument too long	1. Load a fresh aliquot of each patient sample. 2. Repeat the test(s). Be sure the sample is pipetted into the RVs within one hour of loading it onto the instrument. Be sure sample from 3 mL sample containers is pipetted into the RVs within two hours of loading.

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Patient Sample Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Unexpected sample results ***(continued)***	Wrong reagent pack loaded, or placed in an incorrect position on the reagent carousel	1. Verify that the reagent pack was loaded by checking the Supplies screen. If it is missing, load a reagent pack. 2. If the reagent pack is listed on the screen, verify its location by unloading it from the carousel. • If the reagent pack is on-board, but is not presented during this process, contact Technical Support for assistance. • If Technical Support confirms a misplaced reagent pack, retrieve the pack. 3. Reload the reagent pack after you have verified its location. 4. Repeat the test(s).
	Expired reagent pack	1. Check the reagent pack expiration date on the Reagent Inventory screen. 2. Unload the expired reagent pack and load a new one. • If the lot number of the new reagent pack is different than the expired pack, recalibrate the assay. 3. Repeat the test(s).
	Reagent pack unstable or contaminated due to improper handling	1. Unload the reagent pack and load a new reagent pack. • If the lot number of the new reagent pack is different than the removed pack, recalibrate the assay. 2. Repeat the test(s).
	Expired assay calibration	1. Check the **Reagent Pack** button on the Supplies screen. If the lot number is red, the calibration has expired. 2. View the test results. Any test results calculated with an expired calibration will be flagged. 3. Recalibrate the assay. 4. Repeat the test(s).
	Quality Controls (QC) not run after preventive maintenance or repair	1. Run QC. 2. Evaluate any out-of-range QC results according to your established laboratory procedures. 3. Troubleshoot any test result flags, and recalibrate the assay if necessary. 4. Repeat the test.
	Partial bottles of substrate combined	1. Change the substrate bottle and prime the substrate. 2. Repeat the test(s).
	Daily or weekly maintenance not performed	1. Perform daily or weekly maintenance. 2. Repeat the test(s).
	Wrong sample container and/or rack	Load the samples using appropriate sample containers and racks. Be sure that the sample containers are in a rack with the correct rack ID.

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Patient Sample Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Unexpected sample results *(continued)*	Sample container missing or placed in incorrect position in the rack	1. Be sure that the sample containers are in the proper order in the rack. 2. Repeat the test(s).
Sample values are too high	Patient samples evaporating from being on the instrument too long	1. Load a fresh aliquot of each patient sample. 2. Repeat the test(s). Be sure the sample is pipetted into the RVs within one hour of loading it onto the instrument. Be sure sample from 3 mL sample containers is pipetted into the RVs within two hours of loading.
Low sample value flag	Incorrect dilution factor	1. If the sample result was generated with an automated dilution (for example, the Diluted βhCG assay), repeat the sample in the standard assay format (Total βhCG assay). 2. If the results are still too high, contact Technical Support.
	Patient sample handled incorrectly	Be sure that sample is stored and handled according to proper laboratory procedures. Refer to individual assay reagent instructions for use for proper sample handling instructions.
Increased assay variability/poor precision	Wrong reagent pack loaded, or placed in an incorrect position on the reagent carousel	1. Verify that the reagent pack was loaded by checking the Supplies screen. If it is missing, load a reagent pack. 2. If the reagent pack is listed on the screen, verify its location by unloading it from the carousel. • If the reagent pack is on-board, but is not presented during this process, contact Technical Support for assistance. • If Technical Support confirms a misplaced reagent pack, retrieve the pack. 3. Reload the reagent pack after you have verified its location. 4. Repeat the test(s).
Unexpected shift in assay results	Expired reagent pack	1. Check the reagent pack expiration date on the Reagent Inventory screen. 2. Unload the expired reagent pack and load a new one. • If the lot number of the new reagent pack is different than the expired pack, recalibrate the assay. 3. Repeat the test(s).
	Expired assay calibration	1. Check the **Reagent Pack** button on the Supplies screen. If the lot number is red, the calibration has expired. 2. View the test results. Any test results calculated with an expired calibration will be flagged. 3. Recalibrate the assay. 4. Repeat the test(s).

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Patient Sample Troubleshooting (continued)

Symptoms	Possible Causes	Corrective Action
Unexpected shift in assay results *(continued)*	Quality Controls (QC) not run after preventive maintenance or repair	1. Run QC. 2. Evaluate any out-of-range QC results according to your established laboratory procedures. 3. Troubleshoot any test result flags, and recalibrate the assay if necessary. 4. Repeat the test.
	Wash buffer contaminated	1. Contact Technical Support to verify the need to rinse the wash buffer reservoir. 2. If Technical Support confirms, rinse the wash buffer reservoir. 3. If the System Check results are acceptable: • Recalibrate the assay. • Run controls and repeat the test(s). 4. If the System Check results are not acceptable, contact Technical Support.
Increasing values across the run	Patient samples evaporating from being on the instrument too long	1. Load a fresh aliquot of each patient sample. 2. Repeat the test(s). Be sure the sample is pipetted into the RVs within one hour of loading it onto the instrument. Be sure sample from 3 mL sample containers is pipetted into the RVs within two hours of loading.

Test Result Flags

Use the following tables to troubleshoot fatal (no calculated result) or non-fatal (the result was calculated, but a condition exists for that result) test result flags.

NOTE

The system may print the same test result flag twice on a sample report. Ignore the duplicate flag.

Fatal Flags

Fatal Flag	Description	Corrective Action
CCR	A result could not be calculated because: • One of the tests included in a derived result formula did not produce a result. • A confirmatory test result could not be calculated. Usually this occurs because the samples for the qualitative and confirmatory tests were not aspirated at the same time. • Another error prevented the system from calculating a result.	1. Take one of the following actions: • For results other than derived results, skip to step 2. • For derived results, review each test result used in the derived result formula. If a result failed, troubleshoot according to the flag for that result. 2. Review the Event Log and troubleshoot according to the error events with a similar date and time to this event. 3. Repeat the test. • For a derived result, repeat all tests included in the derived result formula. • For a confirmatory result, repeat the confirmatory and qualitative tests. 4. If the problem persists, contact Technical Support.

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Fatal Flags (continued)

Fatal Flag	Description	Corrective Action
CLT	An obstruction was detected.	1. Review the Event Log and troubleshoot according to the error events with a similar date and time to this event. 2. Repeat the test. 3. If the problem persists, contact Technical Support.
IND	• For sandwich assays, the result is at the low end of the analyte concentration curve. The result cannot be distinguished from a system failure because the RLU reading or concentration is too low. • For competitive assays, the result is at either the high or low end of the analyte concentration curve. The result cannot be distinguished from a system failure because the RLU reading or concentration is either too high or too low.	1. Review the Event Log for error events with a similar date and time to this event. • If events occurred, troubleshoot. 2. Run controls, then repeat the test. • If the controls are not in range, troubleshoot. • If you have questions about the result, or if the problem persists, contact Technical Support.
NCR	No calibration data existed for the reagent lot when the result was processed.	1. Calibrate the assay 2. Repeat the test(s).
QNS	The sample volume is insufficient. Additional tests will not be scheduled for this sample. Tests already scheduled will be completed.	1. Follow the troubleshooting instructions for the QNS event in the Event Log. 2. Repeat the test(s). 3. If the problem persists, contact Technical Support.
RLU	The relative light units (RLUs) are outside the acceptable luminometer measuring range.	1. Review the Event Log and troubleshoot according to the error events with a similar date and time to this event. 2. Repeat the test(s). 3. If the problem persists, contact Technical Support.
SYS	A device error occurred during processing.	1. Review the Event Log and troubleshoot according to the error events with a similar date and time to this event. 2. Repeat the test(s). 3. If the problem persists, contact Technical Support.
TRI	The temperature of the incubator was outside the acceptable limits. All tests being incubated when the temperature was outside limits are flagged.	1. Check the incubator temperature on the Maintenance Review screen. If the temperature is outside the acceptable limits, periodically monitor the incubator temperature on this screen until it is within the acceptable limits. • If the system was rebooted or instrument covers were recently opened, you may need to wait up to 30 minutes for the temperature to normalize. • If the system was recently restarted, you may need to wait up to 1 hour for the temperature to normalize. 2. When the incubator temperature is within the acceptable limits, repeat the test(s). 3. If the temperature does not normalize, or if the problem persists, contact Technical Support.

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Fatal Flags (continued)

Fatal Flag	Description	Corrective Action
TRS	The temperature of the substrate was outside the acceptable limits when it was dispensed.	1. Check the substrate temperature on the Maintenance Review screen. If the temperature is outside the acceptable limits, periodically monitor the substrate temperature on this screen until it is within the acceptable limits. • If the system was rebooted or instrument covers were recently opened, you may need to wait up to 30 minutes for the temperature to normalize. • If the system was recently restarted, you may need to wait up to 1 hour for the temperature to normalize. 2. When the substrate temperature is within the acceptable limits, repeat the test(s). 3. If the temperature does not normalize, or if the problem persists, contact Technical Support.
TRW	The temperature of the wash/read carousel was outside the acceptable limits. All tests with RVs in the wash/read carousel when the temperature was outside limits are flagged.	1. Check the wash/read carousel temperature on the Maintenance Review screen. If the temperature is outside the acceptable limits, periodically monitor the wash/read carousel temperature on this screen until it is within the acceptable limits. • If the system was rebooted or instrument covers were recently opened, you may need to wait up to 30 minutes for the temperature to normalize. • If the system was recently restarted, you may need to wait up to 1 hour for the temperature to normalize. 2. When the wash/read carousel temperature is within the acceptable limits, repeat the test(s). 3. If the temperature does not normalize, or if the problem persists, contact Technical Support.

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Non-Fatal Flags

Non-Fatal Flag	Description	Corrective Action
CEX	The calibration curve or cut-off value is expired.	1. Recalibrate the assay. 2. Repeat the test(s).
CRH	The result is above the upper limit of the critical range. Not applicable for QC or Calibrations.	This is a valid test result. No corrective action is necessary.
CRL	The result is below the lower limit of the critical range. Not applicable for QC or Calibrations.	This is a valid test result. No corrective action is necessary.
EXS	The substrate is expired.	1. Change the substrate bottle from the Supplies screen. 2. Repeat the test(s).
GRY	For qualitative assays, the result is within the specified gray zone.	This is a valid test result. No corrective action is necessary.
LEX	The reagent pack lot is expired.	1. Unload the expired reagent pack and load a new one. • If the lot number of the new reagent pack is different than the expired pack, recalibrate the assay. 2. Repeat the test(s).
LRH	The result is above the upper limit of the LIS range. The system does not send results with this flag to the LIS. **Notes:** • This flag is displayed only when the **Auto-Send to LIS** option is set to **Verify**. • This flag is for quantitative assays, semi-quantitative assays, and derived results only.	1. Review the result. 2. Take one of the following actions: • Send the result to the LIS manually. • Delete the result and repeat the test(s).
LRL	The result is below the lower limit of the LIS range. The system does not send results with this flag to the LIS. **Notes:** • This flag is displayed only when the **Auto-Send to LIS** option is set to **Verify**. • This flag is for quantitative assays, semi-quantitative assays, and derived results only.	1. Review the result. 2. Take one of the following actions: • Send the result to the LIS manually. • Delete the result and repeat the test(s).
LOW	The result is lower than the minimum reportable result value defined in the APF.	No corrective action is necessary.
ORH	The result is above the upper limit of the reference range. Not applicable for QC or calibrations.	No corrective action is necessary.
ORL	The result is below the lower limit of the reference range. Not applicable for QC or calibrations.	No corrective action is necessary.

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Non-Fatal Flags (continued)

Non-Fatal Flag	Description	Corrective Action
OVR	The calculated concentration is above the highest or most concentrated calibrator. This flag is only used for quantitative and semi-quantitative assays.	1. Review the Event Log for error events with a similar date and time to this event. • If events occurred, troubleshoot. 2. Take one of the following actions: • If events occurred, and you performed troubleshooting procedures, run controls and then repeat the test. - If the controls are in range, and the test result is reported as greater than the value of the highest calibrator (>X), you may be able to dilute the sample. To identify whether the assay allows dilutions, see the reagent instructions for use. - If the controls are not in range, follow the QC troubleshooting instructions. • If no events occurred, take one of the following actions: - If the test result is reported as >X, you may be able to dilute the sample. To identify whether the assay allows dilutions, see the reagent instructions for use. If dilutions are allowed, dilute and repeat the test. - If dilutions are not allowed, no further action is necessary. 3. If you have questions about the result, or if the problem persists, contact Technical Support.
PEX	The open pack stability time has elapsed for the reagent pack. The system measures this from the time it first punctures the pack.	1. Unload the expired reagent pack and load a new one. • If the lot number of the new reagent pack is different than the expired pack, recalibrate the assay. 2. Repeat the test(s).
QCF	A quality control violates one or more QC rules	1. Display the QC Chart and Data screen to review which criteria is not met. 2. Follow the QC troubleshooting instructions Assay Troubleshooting.
QEX	The quality control lot is expired.	1. Add a new, unexpired quality control. 2. Repeat the test(s).
RFX	The result is from a reflex test.	This is a valid test result. No corrective action is necessary.

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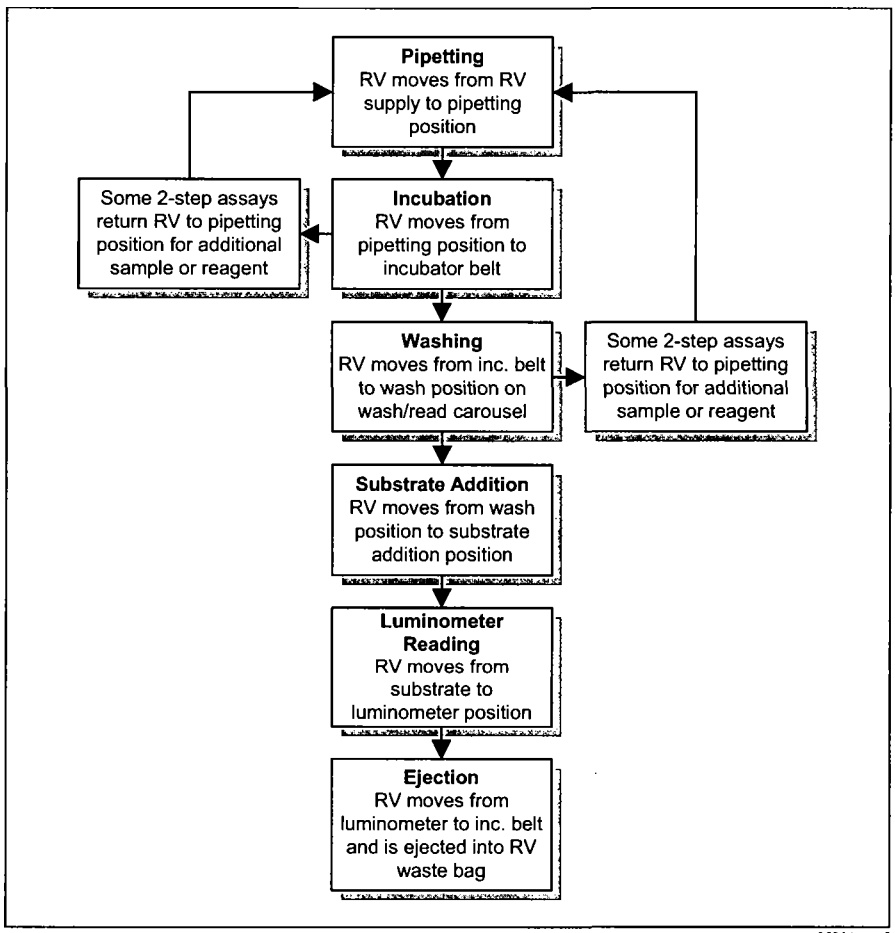
8 Theory of Operation

Samples are processed on the Access 2 system by assigning them a position on a sample rack, entering test requests for those samples, and then loading the sample racks onto the instrument for processing.

Reaction Vessel Transport

The instrument moves the RV through the following stages:



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Assay Calibration Theory

Assay calibrations are used to establish values that the system uses to report test results for patient and quality control samples on an instrument.

To report a test result, the system requires a current calibration for each requested test. The number of calibrators required, the math model, and all other calibration parameters are defined in the assay protocol file (APF) for each assay, and by the information you enter into the system when you set up a new calibrator set.

The Access 2 system performs the following types of assay calibrations:

Quantitative	Calibrator test results provide a multi-point calibration curve. The system uses the calibration curve to convert a measured response in RLUs to an analyte concentration and then expresses the result in numerical units.
Semi-Quantitative	Calibrator test results provide a multi-point calibration curve. The system uses the calibration curve to convert a measured response in RLUs to an analyte concentration and then expresses the result in numerical units. These assays may report their quantitative result as a qualitative interpretation, such as reactive, non-reactive, or equivocal.
Qualitative	Calibrator test results provide a cutoff value based on a predefined formula. The system compares a test result to the cutoff value and then classifies the result as reactive or non-reactive for the analyte.

Calculating Predicted Precision

After an acceptable calibration curve is obtained, the system calculates an error band around the curve. This calculation is based on the distance of the calibration data points from the curve. The system uses the calibration data and the shape of the math model to predict the precision at the predefined analyte concentrations.

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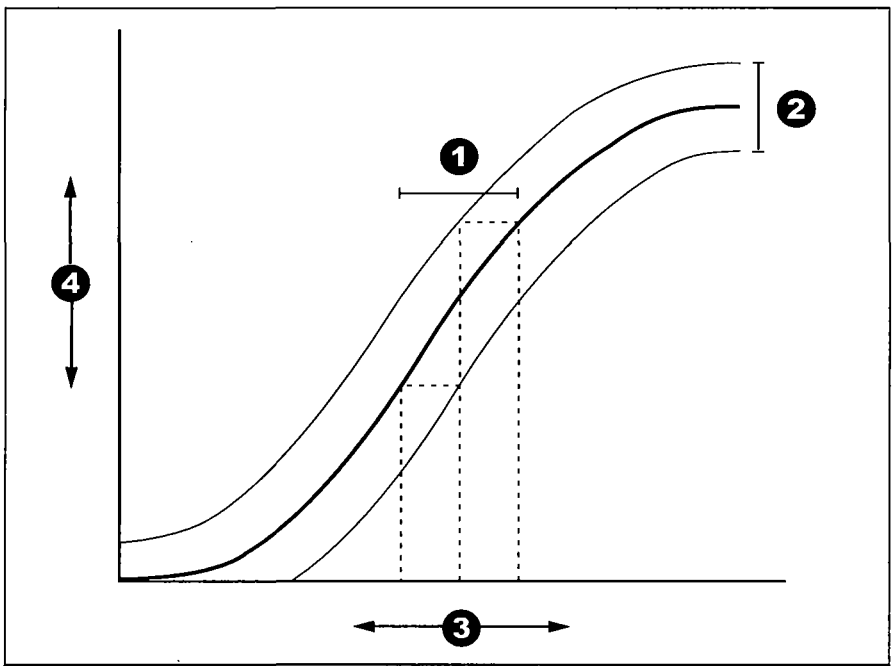
Comparing Predicted Precision to Defined Limits

The system compares the calculated predicted precision to the limits defined in the APF. If the result for any analyte concentration is outside the acceptable limits defined by the error band, the calibration fails.



1	Precision
2	Error Band (the Width of the Error Band is Exaggerated for Illustration Purposes)
3	X Axis: Analyte Concentration
4	Y Axis: RLUs

Calculating Test Results

To determine the analyte concentration in a sample, the system must have a current (accepted) calibration curve. When the patient or quality control sample is tested, the system measures the RLUs and then uses the calibration curve to convert the result to an analyte concentration.

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Obstruction Detection Theory

An Access 2 instrument equipped with a pressure monitor can detect an obstruction in the primary probe while aspirating sample by monitoring the pressure required to draw a sample.

If the pressure required to draw a sample exceeds an accepted threshold, the test is cancelled and flagged with the CLT (obstruction) fatal flag, and an event is logged. If two consecutive failures occur on the same sample, any remaining tests for that sample are cancelled. If five consecutive failures occur, the system stops scheduling tests and goes to the **Not Ready** mode when the tests in progress are completed. The operator must then initialize the system and inspect, clean, or replace the probe as necessary.

Pressure Monitor Reference Curve Determination

The system determines a reference curve for the pressure monitor by measuring the pressure profiles for two different sample volumes. The reference curve is used to identify the expected pressure profile for any given sample volume.

A reference curve is determined when the obstruction detection hardware is installed. Determine a new curve after the main pipettor is cleared of an obstruction; after the main pipettor, pressure sensor, or associated tubing is replaced; when following troubleshooting instructions; or as instructed by a technical support representative.

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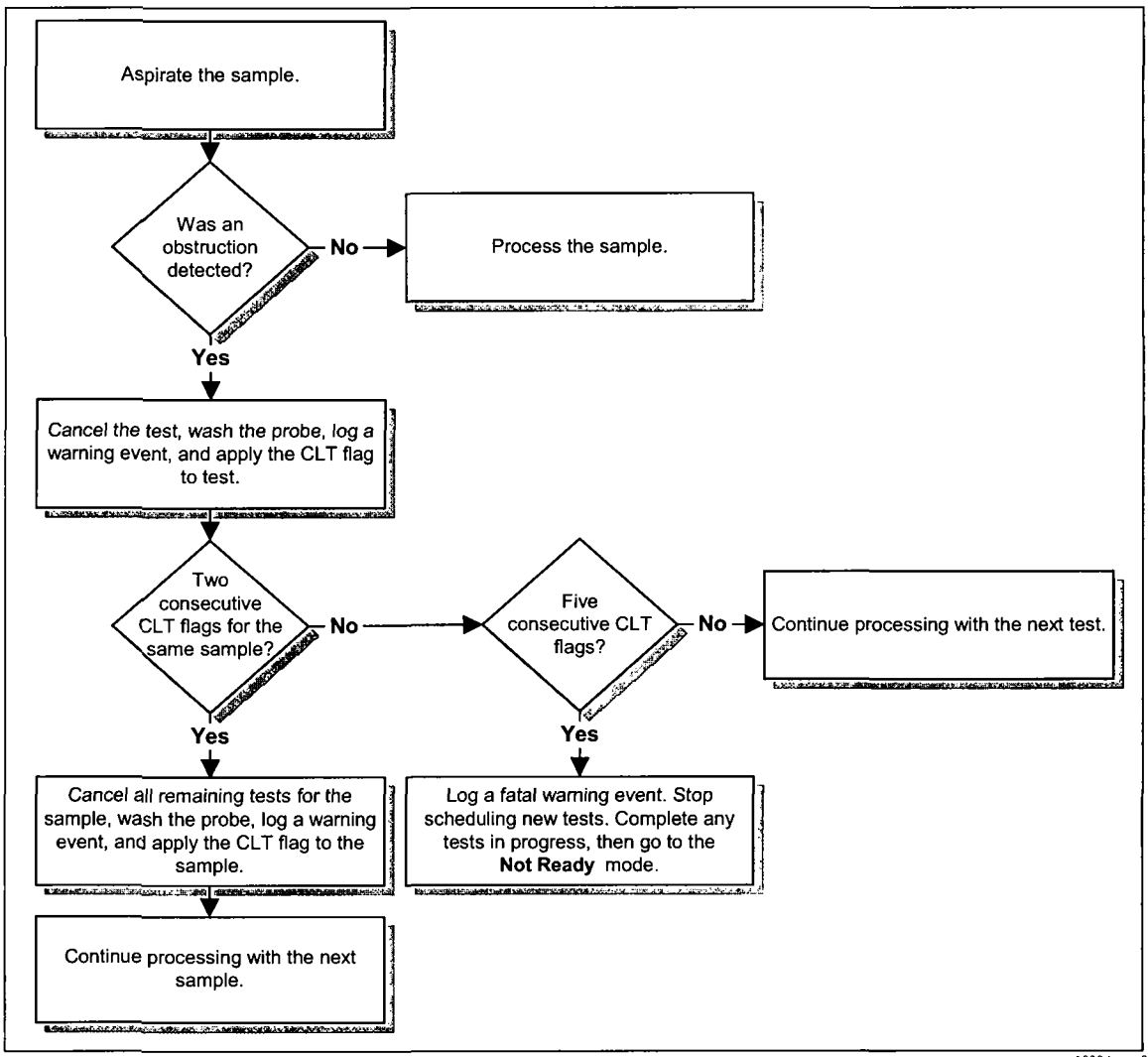
Obstruction Detection Flowchart



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A Ordering Information

Assay-Specific Reagents

The availability of these assays in your country depends on the status of submissions to local regulatory agencies. In addition, an assay may not be available for use on all systems. Contact your Beckman Coulter representative if you have questions about the availability of particular assays.

To obtain assay-specific reagents:

- In the U.S.A. or Canada, contact Beckman Coulter Customer Service at 1-800-526-3821.
- Outside the U.S.A. and Canada, contact your local Beckman Coulter representative.

Assay Panel	Assay	Part #	Description	Volume	# Tests / Calibrations
Adrenal/ Pituitary	Cortisol	33600	Reagent	2 x 50 tests	100
		33605	Calibrator	6 x 4.0 mL	8
		33606	Diluent (S0)	1 x 4.0 mL	
Allergy	Total IgE	35000	Reagent	2 x 50 tests	100
		35005	Calibrator	7 total; S0 @ 6.0 mL S1–S6 @ 4.0 mL	8
		35006	Diluent (S0)	1 x 6.0 mL	
Anemia	EPO	A16364	Reagent	2 x 50 tests	100
		A16365	Calibrator	6 total; S0 @ 10 mL S1–S5 @ 2.5 mL	5
	Ferritin/ Dil-Ferritin	33020	Reagent	2 x 50 tests	100
		33025	Calibrator	6 x 4.0 mL	8
	Folate / RBC Folate	A98032	Reagent	2 x 50 tests	100
		A98033	Calibrator	6 x 4.0 mL	8
		A99250	Diluent (S0)	1 x 4.0 mL	
		A14206	Lysing Agent	2 x 100 mL	
	Intrinsic Factor Ab	387992	Reagent	2 x 50 tests	100
		387993	Calibrator	2 x 4.0 mL	16
		387999	QC	2 levels; 3 x 4.0 mL each	
	sTfR Soluble Transferrin Receptor	A32493	Reagent	2 x 50 tests	100
		A32494	Calibrator	6 total; S0 @ 4 mL S1–S5 @ 2.5 mL	5
		A32495	QC	3 levels; 2 x 2.5 mL each	
	Vitamin B_{12}	33000	Reagent	2 x 50 tests	100
		33005	Calibrator	6 x 4.0 mL	8
		33006	Diluent (S0)	1 x 4.0 mL	
Blood Virus	HAV Ab *	34200	Reagent	2 x 50 tests	100
		34205	Calibrator	5 x 2.0 mL	4
		34209	QC	2 levels; 3 x 3.5 mL each	
	HAV IgM *	34210	Reagent	2 x 50 tests	100
		34215	Calibrator	2 x 1.0 mL	2
		34219	QC	2 levels; 3 x 2.5 mL each	

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Assay Panel	Assay	Part #	Description	Volume	# Tests / Calibrations
Blood Virus (continued)	HBc Ab *	34240	Reagent	2 x 50 tests	100
		34245	Calibrator	2 x 1.0 mL	2
		34249	QC	2 levels; 3 x 2.0 mL each	
	HBc IgM *	34250	Reagent	2 x 50 tests	100
		34255	Calibrator	2 x 1.0 mL	2
		34259	QC	2 levels; 3 x 2.5 mL each	
	HBs Ab *	A24296	Reagent	2 x 50 tests	100
		A24297	Calibrator	6 x 2.5 mL	5
		A24298	QC	2 levels; 3 x 3.5 mL each	
	HBs Ag *	A24291	Reagent	2 x 50 tests	100
		A24292	Calibrator	2 x 2.7 mL	5
		A24294	QC	2 levels; 3 x 4.0 mL each	
	HBs Ag Confirmatory *	A24295	Confirmatory Reagent	2 x 50 tests	100 (50 patient samples)
	HCV Ab PLUS *, †	34330	Reagent	2 x 50 tests	100
		34335	Calibrator	2 x 1.0 mL	2
		34339	QC (Pos/Neg)	2 levels; 3 x 2.5 mL each	
	HIV-1/2 New *, †	34020	Reagent	2 x 50 tests	100
		34025	Calibrator	2 total; C0 @ 3.5 mL; C1 @ 4.5 mL	2
		34029	QC (Pos/Pos)	2 QC; 3 x 4.3 mL each	
	HIV Combo *, †	A59428	Reagent	2 x 50 tests	100
		A59429	Calibrator (Pos/Neg)	2 x 1.7 mL	3
		A59430	QC	3 QC; 2 x 4.4 mL each	
Bone Metabolism	Intact PTH (routine and interoperative)	A16972	Reagent	2 x 50 tests	100
		A16953	Calibrator	6 x 1.0 mL	2
	Ostase (bone alkaline phosphatase)	37300	Reagent	2 x 50 tests	100
		37305	Calibrator	6 x 2.5 mL	5
		37309	QC	2 levels; 4.0 mL each	
	Ultrasensitive hGH	33580	Reagent	2 x 50 tests	100
		33585	Calibrator	6 x 2.0 mL	4
Cardiovascular	AccuTnI	A78803 ** or 33340	Reagent	2 x 50 tests	100
		33345	Calibrator	6 x 1.0 mL	2
	CK-MB	386371	Reagent	2 x 50 tests	100
		386372	Calibrator	6 x 2.0 mL	4
	Digoxin	33710	Reagent	2 x 50 tests	100
		33715	Calibrator	6 x 4.0 mL	8
		33716	Diluent	1 x 4.0 mL	
	Myoglobin	973243	Reagent	2 x 50 tests	100
		973244	Calibrator	6 x 1.0 mL	2
Diabetes	Ultrasensitive Insulin	33410	Reagent	2 x 50 tests	100
		33415	Calibrator	6 x 2.0 mL	4

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Assay Panel	Assay	Part #	Description	Volume	# Tests / Calibrations
Infectious Disease	CMV IgG *	A40702	Reagent	2 x 50 tests	100
		A40703	Calibrator	6 x 1.0 mL	2
		A40704	QC (Pos/Neg)	2 levels; 3 x 2.5 mL each	
	CMV IgM *	A40705	Reagent	2 x 50 tests	100
		A40706	Calibrator	2 levels; 1.0 mL each	2
		A40707	QC (Pos/Neg)	2 levels; 3 x 2.5 mL each	
	Rubella IgG	34430	Reagent	2 x 50 tests	100
		34435	Calibrator	6 x 1.0 mL	2
		34439	QC (Pos/Neg)	2 levels; 3 x 2.5 mL each	
	Rubella IgM *	A32937	Reagent	2 x 50 tests	100
		34445	Calibrator	4 x 1.0 mL	2
		34449	QC (Pos/Neg)	2 levels; 3 x 2.5 mL each	
	Toxo IgG	A31588	Reagent	2 x 50 tests	100
		A31589	Calibrator	6 x 1.0 mL	2
		A31590	QC (Pos/Neg)	2 levels; 3 x 2.5 mL each	
	Toxo IgM II	34470	Reagent	2 x 50 tests	100
		34475	Calibrator	2 x 1.5 mL	3
		34479	QC (Pos/Neg)	2 levels; 3 x 3.5 mL each	
Inflammation	IL-6 *	A16369	Reagent	2 x 50 tests	100
		A16370	Calibrator	6 total; S0 @ 4.0 mL S1–S5 @ 2.5 mL	5
		A16371	QC	3 levels; 2 x 2.5 mL each	
Reproductive	DHEA-S	A10826	Reagent	2 x 50 tests	100
		A10827	Calibrator	6 x 2.0 mL	4
	Estradiol	33540	Reagent	2 x 50 tests	100
		33545	Calibrator	6 total; S0 @ 4.0 mL S1–S5 @ 2.5 mL	5
		33546	Diluent (S0)	1 x 4.0 mL	
	Estriol, Unconjugated	33570	Reagent	2 x 50 tests	100
		33575	Calibrator	7 total; S0 @ 4.0 mL S1–S6 @ 2.5 mL	5
	hFSH	33520	Reagent	2 x 50 tests	100
		33525	Calibrator	6 x 4.0 mL	8
	hLH	33510	Reagent	2 x 50 tests	100
		33515	Calibrator	6 x 4.0 mL	8
	Inhibin A	A36097	Reagent	2 x 50 tests	100
		A36098	Calibrator	7 x 2.5 mL	5
		A36100	QC	3 levels; 2 x 2.5 mL each	
	Progesterone	33550	Reagent	2 x 50 tests	100
		33555	Calibrator	6 total; S0 @ 4.0 mL S1–S5 @ 2.5 mL	5
		33556	Diluent (S0)	1 x 4.0 mL	
	Prolactin	33530	Reagent	2 x 50 tests	100
		33535	Calibrator	6 total; S0 @ 4.0 mL S1–S5 @ 2.5 mL	5

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Assay Panel	Assay	Part #	Description	Volume	# Tests / Calibrations
Reproductive (continued)	SHBG	A48617	Reagent	2 x 50 tests	100
		A48618	Calibrator	6 x 1.0 mL	2
		A48619	QC	2 levels; 3 x 2 mL each	
	Testosterone	33560	Reagent	2 x 50 tests	100
		33565	Calibrator	6 x 2.5 mL	5
	Total βhCG / Diluted Total βhCG	33500	Reagent	2 x 50 tests	100
		33505	Calibrator	6 x 4.0 mL	8
Thyroid	Free T3	A13422	Reagent	2 x 50 tests	100
		A13430	Calibrator	6 x 2.5 mL	5
	Free T4	33880	Reagent	2 x 50 tests	100
		33885	Calibrator	6 x 2.5 mL	5
	hTSH, Fast / HYPERsensitive	33820	Reagent	2 x 50 tests	100
		33825	Calibrator	6 x 4.0 mL	8
	Thyroglobulin	33860	Reagent	2 x 50 tests	100
		33865	Calibrator	6 x 2.0 mL	4
		33866	Diluent	1 x 14.0 mL	
	Thyroglobulin Antibody II	A32898	Reagent	2 x 50 tests	100
		A36920	Calibrator	6 total; S0 @ 4.0 mL S1–S5 @ 2.5 mL	5
	Total T3	33830	Reagent	2 x 50 tests	100
		33835	Calibrator	6 x 4.0 mL	8
	Total T4	33800	Reagent	2 x 50 tests	100
		33805	Calibrator	6 x 4.0 mL	8
	Thyroid Uptake	33810	Reagent	2 x 50 tests	100
		33815	Calibrator	1 level; 6 x 1.0 mL	12
	TPO Antibody	A12985	Reagent	2 x 50 tests	100
		A18227	Calibrator	6 x 2.0 mL	4
Tumor Markers	AFP / Dil-AFP	33211	300 test kit (Cals included)	6 x 50 tests Cals: 7 x 2.5 mL	300 5
		33210 *	100 test kit (outside US only)	2 x 50 tests	100
		33215 *	Calibrator (for 100 test kit)	7 x 2.5 mL	5
		33216	Diluent	1 x 14.0 mL	
		33219	QC	3 levels; 2 x 4.0 mL each	
	BR Monitor (cancer antigen 15-3)	387620	Reagent	2 x 50 tests	100
		387647	Calibrator	6 x 1.5 mL	3
	CEA	33200	Reagent	2 x 50 tests	100
		33205	Calibrator	6 x 2.5 mL	5
		33206	Diluent	1 x 4.0 mL	
		33209	QC	2 levels; 3 x 2.5 mL each	
	GI Monitor (cancer antigen 19-9)	387687	Reagent	2 x 50 tests	100
		387688	Calibrator	6 x 2.5 mL	5
	Hybritech PSA	37200	Reagent	2 x 50 tests	100
		37205	Calibrator	6 x 2.5 mL	5
		37206	Diluent	1 x 14.0 mL	
		37209	QC	3 levels; 5.0 mL each	

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Assay Panel	Assay	Part #	Description	Volume	# Tests / Calibrations
Tumor Markers *(continued)*	Hybritech free PSA	37210	Reagent	2 x 50 tests	100
		37215	Calibrator	6 total; S0 @ 5.0 mL S1–S5 @ 2.5 mL	5
		37219	QC	2 levels; 5.0 mL each	
	Hybritech p2PSA ††	A49752	Reagent	2 x 50 tests	100
		A49753	Calibrator	7 x 2.1 mL	4
		A56934	QC	3 levels; 5.0 mL each	
	OV Monitor (cancer antigen 125)	386357	Reagent	2 x 50 tests	100
		386358	Calibrator	6 x 2.5 mL	5
Research Use Only (RUO)	IL-6 (RUO)	A30945	Reagent	2 x 50 tests	100
		A30944	Calibrator	6 total; S0 @ 4.0 mL S1–S5 @ 2.5 mL	5
		A30946	QC	3 levels; 2 x 2.5 mL each	

* Not available in the U.S.
† Sold by Bio-Rad for use on Beckman Coulter immunoassay systems. Bio-Rad is a trademark of Bio-Rad Laboratories, Inc.
** The AccuTnI reagent available in your country depends on the status of registration with local regulatory agencies.
†† In development for the U.S. market, pending FDA approval.

System Supplies

System supplies are organized alphabetically in two tables. The first table contains supplies ordered through Customer Service. The second table contains supplies ordered through Technical Support.

To obtain the following supplies:

- In the U.S.A. or Canada, contact Customer Service at 1-800-526-3821.
- Outside the U.S.A. and Canada, contact your local Beckman Coulter representative.

System Supply Description	Part #	Quantity
Aspirate probe supplies:		
Aspirate probe, stainless steel universal	8409B *	1
Aspirate probe cleaning kit	80769	(Syringe, fitting assembly, and 10 brushes)
Aspirate probe brushes, disposable	973001	10
Citranox † acid cleaner and detergent	81912	1 gallon
Contrad † 70 cleaning solution	81911	1 liter
Data storage devices: **		
Travan † 8 GB tape **	973087	1
Travan 20 GB tape **	386175	1 box of 3 tapes
Travan 40 GB tape **	A38447	1 or 3 tapes
USB 8 GB Flash Drive **	A81923	1
Printer supplies are no longer available from Beckman Coulter, Inc. Obtain printer supplies from your local office supplier or the printer manufacturer.		
Reaction vessel cartridges	81901	16 @ 98 vessels each
Sample Diluent A	81908	1 x 4 mL

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System Supply Description	Part #	Quantity
Sample containers		
0.5 mL sample cups, Beckman Coulter	651412	1000
1.0 mL/13 mm insert cups, Beckman Coulter	81915	1000
1.0 mL/13 mm insert cup caps	81920	1000
2.0 mL/13 mm sample cups, Beckman Coulter	81902 or 652730	1000
2.0 mL/16 mm insert cups, Beckman Coulter	81917	1000
3.0 mL sample containers, Beckman Coulter	81914	500
3.0 mL sample container caps	81922A *	1000
Autoaliquot tubes (13x100 mm false bottom), Beckman Coulter	2910034	4000
Pediatric insert cups, 1.0 mL, Beckman Coulter	81916	1000
Pediatric tube adapters for 13 mm rack, Beckman Coulter	472987	100
Sample racks:		
13 mm	81606	6
16 mm x 100 mm	81608	6
16 mm x 75 mm Elevated	81609	6
Sample rack bar code label kit	973099	57 bar code label
Substrate	81906	4 @ 130 mL each
Swab applicators, fiber-free polyester	104838	100
System Check Solution	81910	6 @ 4 mL each
Wash buffer II, Access	A16792	4 @ 1950 mL each
Waste bags, reaction vessel	81904	20

* An item with a part number ending in a letter may be revised from time to time. If you have difficulty ordering this item, ask your Beckman Coulter representative to check for a more recent revision.

† Citranox is a trademark of Alconox, Inc.
Contrad is a trademark of Decon Laboratories, Inc.
Travan is a trademark of Imation Corp.

** Be sure to order the appropriate data storage device for your Access 2 system. Storage devices are not interchangeable. Contact Technical Support if you cannot determine which storage device to order for your system.

To obtain the following supplies:

- In the U.S.A. or Canada, contact Technical Support by phone at 1-800-854-3633.
- Outside the U.S.A. and Canada, contact your technical support representative.

System Supply Description	Part #	Quantity
CARE Kit	973077	1
Keyboard templates:		
English	973041	1
French	973254	1
German	973256	1
Italian	973257	1
Spanish	973255	1
Manuals / System Documentation:		
Assay Manual CD-ROM (Multilingual)	A35426	1
Installation Implementation Guide; Paper, with binder	973265	1
LIS Vendor Information document CD-ROM; English	387848	1
Maintenance and Service Log; Paper, with binder	973266	1

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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x x x COMMUNICATION RESULT REPORT (JUN. 18. 2013 3:01PM) x x x

FAX HEADER 1:
FAX HEADER 2:

TRANSMITTED/STORED : JUN. 18. 2013 2:42PM FILE MODE	OPTION	ADDRESS	RESULT	PAGE
5561 MEMORY TX		BECKMAN COULTER	OK	3/3

REASON FOR ERROR
E-1) HANG UP OR LINE FAIL
E-2) BUSY
E-3) NO ANSWER
E-4) NO FACSIMILE CONNECTION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

June 14, 2013

Beckman Coulter, Inc.
C/O Kerrie Oetter
1000 Lake Hazeltine Drive
CHASKA MN 55318-1084

Re: K121214
Trade/Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: II
Product Code: MMI, JIT, JJE
Dated: June 04, 2013
Received: June 06, 2013

Dear Ms. Oetter:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

COVER SHEET MEMORANDUM

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics and
Radiological Health

From: Reviewer Name Paula Caposino

Subject: 510(k) Number k121214

To: The Record

Please list CTS decision code: SE

☐ Refused to Accept (Note: this is considered the first review cycle. See screening checklist.)

☐ Hold (Additional Information or Telephone Hold)

☒ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.)

Please complete the following for a final clearance decision (i.e, SE, SE with Limitations, etc.)	YES	NO
Indications for Use Page *(Attach IFU)*	X	
510(k) Summary or 510(k) Statement *(Attach Summary or Statement)*	X	
Truthful and Accurate Statement *(Must be present for a Final Decision)*	X	
Is the device Class III?		X
Does firm reference standards? (If yes, please attach Form 3654.)	X	
Is this a combination product?		X
Is this a reprocessed single use device? (See Guidance for Industry and FDA Staff - MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices.)		X
Is this device intended for pediatric use only?		X
Is this a prescription device? (If both prescription & OTC, check both boxes.)	X	
Is clinical data necessary to support the review of this 510(k)?	X	
For United States based clinical studies only, did the application include a completed Form FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank? (If study was conducted in the United States and Form FDA 3674 was not included or was incomplete, then applicant must be contacted to obtain completed form.)	X	
Does this device include an Animal Tissue Source?	X	
All Pediatric Patients age <= 21		X
Neonate/Newborn (Birth to 28 days)		X
Infant (29 days to < 2 years)		X
Child (2 years to <12 years)		X
Adolescent (12 years to <18 years)		X
Transitional Adolescent A (18 years to <21 years); Special considerations are being given to this group, different from adults age >= 21 (different device design or tesating, different protocol procedures, etc.)		X
Transitional Adolescent B (18 years to <21 years); No special considerations compared to adults >= 21 years)		X

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Nanotechnology		X
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance)		X

egulation Number:	21 CFR 862.1215
Class:	II
Product Code:	MMI
Additional Product Codes:	JIT, JJE

Digital Signature Concurrence Table
(Not all signatures may be required)

Branch Chief Sign-Off	Ruth A. Chesler -S 2013.06.14 09:54:24 -04'00'
Division Sign-Off	Courtney H. Lias, Ph.D. 2013.06.14 13:03:34 -04'00'

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** _Ian Pilcher_____

I. Product Data

Panel Code: 75 **Product Code:** MMI	**Device Name:** Access® Immunoassay Systems AccuTnI Reagent Kit when used in conjunction with UniCel DxI Access Immunoassay Systems
Model: Reagent: A78803, 33340; Calibrators: 33345	**Lot/Serial Numbers:** All lots

Marketing Status (Include 510(K) or PMA Number, Specify if Exempt From 510(K) :
k010429, k021814

Total Number of Devices In Distribution: 196,071

U.S.: 184,110 **Foreign:** 11,961

Number of Devices Subject to Recall or Review: 196,071

U.S.: 184,110 **Foreign:** 11,961

Manufacturer / Recalling Firm, Address:
Beckman Coulter, Inc.
250 S. Kraemer Blvd.
Brea, California 92821, USA

Product Description (Include Intended Use from labeling or known off-label uses):
The product being recalled is the Access® Immunoassay Systems AccuTnI Reagent Kit when used in conjunction with UniCel DxI Access Immunoassay Systems.

The manufacturer claims the following intended use: The Access® AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access Immunoassay Systems to aid in the diagnosis and treatment of myocardial infarction and cardiac muscle damage. Cardiac Troponin I determination also aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

RES · 54729

RCL · 100161 CLASS II

34

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: 54729 **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** Ian Pilcher

II. Problem Definition and Analysis

Reason for Recall or Risk Assessment

- **Description of the Defect, Malfunction or Error in Use of the Device:**
  Beckman Coulter has confirmed customer reports that different results have been obtained from the same patient samples assayed on Access/Access 2 and UniCel DxI platforms. This is a system issue and occurs with all lots of Troponin Reagent when used in conjunction with this analyzer. Values obtained using UniCel DxI systems demonstrate a positive bias when compared to values obtained with Access® or Access® 2 systems. Troponin I test results when assayed with AccuTnI Reagent (REF 33340 and A78803) run on the UniCel DxI system have been shown to have a positive bias up to 48% when compared with results run on the Access/Access 2 systems.

- **Root Cause of the Problem (If Known):**
  The root cause is unknown and an investigation is in process.

- **Factors that May Contribute to Product Risk (i.e. Device Design, Manufacturing Problems or User Error):**
  The AccuTnI reagents have been modified several times since they received 510(k) clearance. FDA believes that some of these modifications required 510(k) clearance, but Beckman Coulter did not submit a 510(k) or notify FDA of these changes. Since FDA did not receive 510(k) submissions for the modified reagents, the performance of the device currently in distribution has not been reviewed to determine if it is substantially equivalent to a cleared device.

  Incorrect troponin test results may lead to incorrect diagnosis of acute myocardial infarction and inappropriate risk stratification of unstable angina and non-ST segment elevation acute coronary syndrome.

- **If Device Failure Occurs is it Easily Recognized by User?**
  No, this malfunction is not easily recognized unless they also test the sample on another analyzer. This malfunction does not appear to cause quality control samples to fail.

Manufacturer's CAPA Investigation (If Available):

- **Summary:**
  None submitted. CAPA in progress.

- **Date of Analysis:**
  Not applicable

- **Firm's Estimate of Number of Devices that will Develop the Defect and/or Fail :**

  - **How Many Devices from the Affected Lots Are Expected to Have or Develop the Defect?**
    All of the devices from the affected lots are expected to develop the defect when used on the DXI system.

  - **How Many Devices with the Defect are Likely to Exhibit the Failure over the Lifetime of the Device?**
    All devices are will to exhibit the failure.

  - **Of Those Devices that Fail, How Many are Likely to Cause Injury if Used?**
    The firms Health Hazard stated that the frequency of occurrence ranged from remote (defined by firm as

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<0.02 per year) to frequent (defined by firm as ≥1 but <10 per year).

- **Any Comments on How these Estimates were Reached:**
  The firm did not define how they reached these estimates.

- **Firm's Conclusion About Health Risk. (Attach a Copy of Firm's HHEs or HHAs):** The firm's documentation evaluated the following patient risks and associated hazards due to falsely elevated results on the DxI:
  - Patient is monitored longer due to false positive results. (Initial or in serial samples). Hazard: Patient is subjected to repeat testing and unnecessary specimen redraws.
  - Patient is given cardiac medications due to false positive results. (Initial or in serial samples). Hazard: Patient is exposed to unnecessary drugs. Recommended drug therapies carries inherent risks including severe bleeding.
  - False positive results. (initial or for serial samples) Hazard: Patient is subjected to repeat testing and unnecessary specimen redraws. Patient is inconvenienced by unnecessary hospital stay and medical expenses.
  - Patient is given diagnostic catheterization due to incorrect false positive results. (initial or for serial samples) Hazard: Patient is subjected to unnecessary invasive procedure.

  The firm's Hazard analyses listed multiple risk mitigation factors for these false positive results. These included the following in clinical practice: Some labs will repeat high measurements, there are clinical studies showing low risk from a low shift above the 99% URL, serial draws are used for clinical assessment, and most labs designate one system for TnI.
  They also stated that QC failures will alert customers of system bias issue, limits for total allowable error include platform bias, and clinical decision points are established as one time events, while system bias is an evaluation of trends (day to day QC).
  Additionally, they stated that bias at dose levels <0.04 ng/mL are considered negative and may be below the lower limit of detection and that the AccuTnI results should be interpreted in light of the total clinical presentation of the patient and should not serve as a stand alone diagnostic measure.
  Based on the factors above, the firm concluded that the risk caused by the defect is acceptable and define it as "as low as reasonably practicable".

- **Any FDA Comments:** FDA believes that the performance of this device has not been fully characterized. The manufacturer has made significant modifications to the reagents without notifying FDA, so FDA has not reviewed the modified reagents for safety and effectiveness or made a determination that the current device is substantially equivalent.
  FDA also believes that the falsely elevated results caused by this defect have the potential to subject patients to serious risk. Most facilities will only run this test on one analyzer, and if the analyzer is the DxI, then they will not know that the result is biased compared to the Access and they may act upon the biased result. In the worst case scenario, this may lead to unnecessary cardiac catheterization. This is an invasive procedure that is not without serious risk to the patient. It should be noted that in the risk control section of the firm's health hazard analysis, they state that QC will detect the bias, but this is only applicable to facilities running AccuTnI on the DxI and Access analyzers. Additionally, FDA believes that TnI results can be used as the primary piece of data in making patient treatment decisions, which raises the risk of unnecessary procedures being performed or medications given. It should also be noted that the bias, which has an average of 30% but has been seen up to 48%, will be seen on every TnI evaluation performed. The fact that every TnI result will be falsely elevated greatly increases the risk associated with this defect.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: 54729 **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** Ian Pilcher

Adverse Events, Complaints and Problems or Incidents that may be Related to the Device Defect:

Number of Complaints 47 **Malfunction Reports** 47

Injuries Reported **U.S.** 0 **International** 0

Deaths Reported **U.S.** 0 **International** _____

0

Sources:

Manufacturer x **Inspection** _____ **MDR's** _____

Explanation:
The manufacturer has reported 47 complaints with no adverse events reported.

Describe the Complaints and Injuries Reported to Date:
The firm reported to have received 47 customer complaints of positive bias in results with no adverse events. One of these reports documented a physician's concern that multiple results above the upper reference limit were reported.

37

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** _Ian Pilcher_____

III. Health Risks

TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

THE FOLLOWING ASSESSMENT IS BASED ON CURRENTLY AVAILABLE INFORMATION. CONCLUSIONS MAY CHANGE IF ADDITIONAL INFORMATION BECOMES AVAILABLE IN THE FUTURE.

Immediate and Long Range Health Consequences:

A. **Describe the Immediate and Long Range Health Consequences (Injuries or Illnesses) That May Result from Use of or Exposure to the Defective Device. (Include Known Off Label Uses)** Troponin is used as an essential piece of diagnostic information in the differential diagnosis of acute chest pain, shortness of breath, traumatic and post-operative cardiac injuries, in short, for the diagnosis of cardiac muscle injury. Troponin is also part of several prognostic and risk algorithms for longer term prognosis of patients with various conditions that can cause cardiac injury.

B. **Describe Any Factors That May Mitigate the Risk:** In the past, CPK-MB enzymes were measured concurrently with troponin levels. However, many clinical laboratories only measure troponin and have discontinued CPK-MB. CPK-MB used to be helpful as a separate diagnostic check on troponin assay performance. Although serial sampling for troponin detecting rising levels of troponin can be a mitigation with false elevation of troponin around the cutpoint, a single elevated troponin level together with a clinical history of chest pain (cardiac or non-cardiac in origin) may tip the balance to send a patient for catheterization in the interest of "saving myocardium" by earliest intervention. Electrocardiographic findings of acute changes can mitigate false positive troponin effects, but clinicians are taught that the electrocardiographic findings of cardiac injury may lag in time behind troponin elevation and electrocardiographic findings may be less sensitive to cardiac injuries that are less in extent than a full STEMI myocardial infarction.

C. **What Segment of the Population is Most at Risk? (e.g. Infants, Elderly, Pregnant Women, Critically Ill Patients, Immunocompromised, etc.)** Any patient who is being clinically evaluated for cardiac injury. The majority will be middle-aged to elderly adults, but some physicians may order troponin on the pediatric age group.

D. **Does the Health Consequence Have Significant Public Health Impact Beyond Users (e.g. Spread of Serious Infection to Others)?** No.

Assess the Hazards Associated with Use of the Defective Product

Check All that Might Occur:

Population at Greatest Risk	Overall Population Using Device	
x	☐	Life-threatening (death has or could occur)

38

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ ORACLE #: _____ RECALL # (s): _____

Date: _____ (Month DD, YYYY) Safety Officer: _Ian Pilcher_____

x	x	Results in permanent impairment of body function or permanent damage to a body structure.
x	x	Necessitates medical or surgical intervention.
x	x	Temporary or reversible (without medical intervention).
x	x	Limited (transient, minor impairment or complaints).
☐	☐	No adverse health consequences.

Explanation: The estimation of hazard is based on the worst case scenario that a false positive, elevated troponin level could recommend a patient for unnecessary cardiac catheterization or thrombolysis therapy. These invasive therapies carry the potential for life threatening complications. While not common, the potential for these complications is only tolerated when there is a potential benefit to the patient for these invasive therapies. There is no benefit to the invasive therapies in the case of a false positive troponin result.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** _Ian Pilcher_____

IV. PROBABILITY

TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

Assess the Probability that Use of, or Exposure to, Product under Recall will Cause

A. Serious Adverse Health Consequences or Death

	Overall Population Using Device	Population at Greatest Risk
Reasonable Probability	☐	x
Remote Probability	x	☐
Not Likely	☐	☐

Explanation / Comments: This estimate of serious adverse health consequence or death is based on the scenarios described under the estimation of hazard.

B. Temporary or Medically Reversible Adverse Health Consequences

	Overall Population Using Device	Population at Greatest Risk
May Cause	x	x
Not Likely to Cause	☐	☐

Explanation / Comments: If the elevated troponin results are not near the cutpoint, the false elevation of troponin level may not change the medical decisions in patients with "true" myocardial injury that will elevate the troponin levels beyond the upper limit of normal + the amount of positive bias in this troponin assay.

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Date: _____ (Month DD, YYYY) Safety Officer: _Ian Pilcher_____

Signatures	Date	Printed Name, Title and Office
Max Robinowitz MD	March 19, 2010	Max Robinowitz, MD, OIVD/DIHD
Ian Pilcher	March 19, 2010	Ian Pilcher, CSO, OIVD/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

I. Product Data

Panel Code:	75	**Device Name:**	Access® Immunoassay Systems (Access, Access 2, LXi 725) UniCel® DxI 800 Access® Immunoassay Systems UniCel® DxI 600 Access® Immunoassay Systems UniCel DxC 600i, 660i, 680i, 860i, 880i SYNCHRON® Access® Clinical Systems
Product Code:	JJE		
Model:	Access: 81600 Access2 : 81600N DxC600i: A25656 LXi 725: 386200 DxI 800: 973100 DxI 600: A30260 DxC 660i: A64871 DxC 680i: A64903 DxC860i: A64935 DxC 880i: A59102	**Lot/Serial Numbers:**	All devices are affected

Marketing Status (Include 510(K) or PMA Number, Specify if Exempt From 510(K) :
k922823, k023049, k023764, k060256, k042291

Total Number of Devices In Distribution: 14,401

U.S.: 4,023 **Foreign:** 10,378

Number of Devices Subject to Recall or Review: 14,401

U.S.: 4,023 **Foreign:** 10,378

Manufacturer / Recalling Firm, Address:
Beckman Coulter, Inc.
250 S. Kraemer Blvd., MS/A2.SW.01
Brea, CA, 92821, USA

Product Description (Include Intended Use from labeling or known off-label uses):
The Access/DxI Immunoassay System is an in vitro diagnostic device used for the quantitative, semi-quantitative or qualitative determination of various analyte concentrations found in human body fluids.

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II. Problem Definition and Analysis

Reason for Recall or Risk Assessment

- **Description of the Defect, Malfunction or Error in Use of the Device:**
  The manufacturer reported that some Access immunoassays are affected by ambient temperature changes and can produce inaccurate results when a system is operated within the published range. The published range specifies that the instrument can be operated properly in an ambient temperature range of 18°C to 32°C. However, Beckman Coulter is now reporting that ambient room temperature changes within the published range above may affect assay results. The magnitude of the inaccuracy varies for each affected analyte and ranges from 1.25% to 4.25% per degree C change in ambient room temperature and the affected assays can be either falsely elevated or falsely reduced depending on the change in ambient temperature and the analyte in question.

  The %change in result per degree C for each analyte are shown below:

  Access Analytes

Analyte	%change / °C
TnI	3.5
BNP	3.5
Cortisol	1.5

  UniCel DxI Analytes

Analyte	%change / °C
Vitamin B12	2.0
AFP	2.5
Estradiol	1.5
Testosterone	2.75
Ultrasensitive hGH	1.75
Cortisol	1.5
Fast TSH	1.75
Free T4	2.0
Rubella IgG	2.75
BNP	4.25
CK-MB	1.25
TPO	2.75
Free T3	3.25
Intraoperative PTH	4.25
Toxo IgG	2.75
Inhibin A	2
SHBG	4

- **Root Cause of the Problem (If Known):**
  Temperature affects the binding kinetics of immunoassays and can cause shifts of the (relative light units) RLU signal and dose. The reason for the current specification of the operating temperature range in the instructions for use is under CAPA investigation.

- **Factors that May Contribute to Product Risk (i.e. Device Design, Manufacturing Problems or User Error):**
  The device labeling states that the analyzer can be operated properly across a temperature range of 18°C to 32°C.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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so users would not suspect that changes in temperature would affect results and would be unlikely to question these erroneous results. Also, QC samples are not regularly run during the middle of shifts, so any affect on results due temperature change within a shift would not be detected by QC.

- **If Device Failure Occurs is it Easily Recognized by User?**
  Device failure will only be recognized by the user if the change in temperature is large enough to cause QC results to fall outside the expected range and this temperature change occurs at a time when QC samples will be run. Otherwise the user is unlikely to recognize the failure.

Manufacturer's CAPA Investigation (If Available):

- **Summary:**
  PAS200200190, and CAPA 5302 contain the complaint investigations into the thermal effects on the Access AccuTnI assay. The firm's investigation makes the following claims:
  1. The maximum deviation from the true AccuTnI value would be a shift of up to 0.02 ng/mL for patient sample at the 0.04 ng/mL URL at the extremes of the current specified operating temperature range.
  2. From the stated IFU the 95% CI at concentration of the 99th percentile URL (0.04 ng/mL) is 0.03 to 0.05ng/mL. At the extremes of the current specified operating temperature range the maximum expected shift for a sample at the 99th percentile URL (0.04ng/mL) would be up to 0.02 ng/mL. This would result in a dose of 0.02ng/mL.
  3. The thermal effect of the Access AccuTnI assay does not "calibrate out." That is, recalibrating at a different temperature does not correct the bias.
  4. All but one of the commercial QC materials used in the investigation are sensitive to temperature changes, providing a good indicator of large temperature shifts. The one exception found so far is a Beckman Coulter control product, which is being discontinued.

- **Date of Analysis:**
  The CAPA is currently ongoing

- **Firm's Estimate of Number of Devices that will Develop the Defect and/or Fail :**

  - **How Many Devices from the Affected Lots Are Expected to Have or Develop the Defect?**
    All affected devices are expected to have the defect.

  - **How Many Devices with the Defect are Likely to Exhibit the Failure over the Lifetime of the Device?**
    All of the devices will exhibit the defect over the lifetime of the device.

  - **Of Those Devices that Fail, How Many are Likely to Cause Injury if Used?**
    The firm's HHE stated that there is a reasonable probability that false low troponin result could lead to a serious adverse health consequence if it were reported by a laboratory. However the firm claims that the probability of a lab reporting a false negative troponin result is low. The firm did not provide any estimation of the likelihood of injury due to erroneous results from any of the other affected analytes.

  - **Any Comments on How these Estimates were Reached:**
    The firm did not report how they reached these estimates.

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RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

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- **Firm's Conclusion About Health Risk. (Attach a Copy of Firm's HHEs or HHAs):** The firm only reported on the health risk of a false negative troponin report, and they concluded that the risk of this malfunction is as follows:
  - For women and others with atypical occult cardiac disease, an untreated myocardial infarction due to a false negative TnI result could lead to life threatening or permanent cardiac damage.
  - In the overall population for whom TnI is ordered, a delay in treatment of myocardial infarction due to a false negative TnI result could lead to permanent cardiac damage.

- **Any FDA Comments:** The firm's HHE did not address the risk of falsely elevated troponin results or of false results with any of the other affected analytes.

Adverse Events, Complaints and Problems or Incidents that may be Related to the Device Defect:

Number of Complaints 29 **Malfunction Reports** 0

Injuries Reported **U.S.** 0 **International** 0

Deaths Reported **U.S.** 0 **International** 0

Sources:

Manufacturer _____ **Inspection** _____ **MDR's** _____

Explanation:

The manufacturer stated that retrospective analysis of complaint records since 2/27/2003 showed a total of 29 complaints that may be due to thermal sensitivity. No injuries have been reported.

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Describe the Complaints and Injuries Reported to Date:

The manufacturer provided the following summary of injuries and complaints:

Event period from 2/27/2003 through 1/18/2011. Four complaints involved erroneous patient results. Three complaints indicated that erroneous results were reported outside of the lab.

1. The complaint investigation indicated that the lab had recently relocated the instrument to a new space with low ceiling near multiple AC vents, a deviation from the Beckman Coulter installation instructions, and that the results may have been due to cooling in the lab. The lab reported marginally high results to the physicians.
2. Patient results from another lab that varied from 27.5°C to 31°C did not misclassify the patient.
3. A complaint indicated that lab temperature conditions were above the instrument operating range at the time. The patient data were not provided.
4. A lab reported that patient results were marginally elevated, but the magnitude of error did not misclassify the patients. Information on lab temperature conditions was not provided.

The remaining customer complaints involved QC results that shifted due to change in lab temperature, possibly caused by the conditions listed below:

☐ Construction in lab
☐ Lab AC shut down
☐ Lab AC blowing directly on instrument

In these cases QC results sometimes returned within range after normal temperature conditions were restored in the lab or instruments were moved out of direct air flow. There were no cases reported where false low erroneous TnI results were large enough to misclassify a patient from significant cardiac risk to no cardiac risk in all 29 complaints.

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Date: _August 30, 2011 Safety Officer: _Ian Pilcher

III. Health Risks **TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE**
THE FOLLOWING ASSESSMENT IS BASED ON CURRENTLY AVAILABLE INFORMATION. CONCLUSIONS MAY CHANGE IF ADDITIONAL INFORMATION BECOMES AVAILABLE IN THE FUTURE.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Date: _August 30, 2011 Safety Officer: _Ian Pilcher

Immediate and Long Range Health Consequences:

A. **Describe the Immediate and Long Range Health Consequences (Injuries or Illnesses) That May Result from Use of or Exposure to the Defective Device. (Include Known Off Label Uses)**

This recall involves a wide spectrum of analytes ranging from low volume, low risk to high volume, high risk analytes. Since it is beyond the scope of this health assessment to consider all possible health consequences related to erroneous results stemming from every analyte under this recall, the highest risk analyte(s) will be considered here for purposes of risk assessment. An *ad hoc* HHE committee was convened and after thorough discussion and debate, it was determined that the highest risk analyte that comes under this recall is the Access TnI (troponin I) assay. Other analytes were considered including intra-operative parathyroid hormone (iPTH) and BNP. Erroneous iPTH levels could certainly lead to significant health consequences (unnecessary removal of additional glands, additional surgical time due to further neck exploration, missed diseased gland(s) leading to the need for additional surgery); however, it is felt that erroneous cTnI levels would result in more acute and significant health consequences. Additionally, it was concluded that while erroneous BNP results could lead to misdiagnosis of congestive heart failure and erroneous prognostic/risk interpretations, this biomarker lacks the acute and urgent clinical significant of troponin values.

Cardiac troponin I (cTnI) is one of several cardiac biomarkers that can be used to aid in the diagnosis of myocardial damage/infarction (MI) – others include cardiac troponin C, cardiac troponin T, CK-MB, and myoglobin. Typically these biomarkers are ordered in the setting of other clinical indicators of disease such as chest pain and/or EKG changes suggesting acute myocardial damage. In isolation, erroneous results could lead to missed diagnosis, misdiagnosis and/or improper treatment of a life-threatening process/event. In the event of erroneous results, i.e. falsely elevated, immediate health consequences would include treating unnecessarily with procedures (i.e. cardiac catheterization) or medications (thrombolytic, anticoagulants) that carry a significant risk profile. A more significant error such as a false negative cTnI measurement could result in a missed diagnosis of cardiac injury, i.e. cardiac ischemia/myocardial infarction. Such missed diagnoses could lead to significant health risk including irreversible cardiac injury and death.

B. **Describe Any Factors That May Mitigate the Risk:**

1. While calibration and using Beckman Coulter (BC) quality control materials will not pick up the device defect due to the fact that the products are not sensitive to ambient temperature changes, using outside commercial QC materials (non-BC products) will allow for detection of the defect as these outside products are susceptible to the ambient temperature changes. However, QC samples are not regularly run during the middle of shifts, so any affect on results due temperature change within a shift would not be detected by QC.

2. Based on the CAPA investigation (see summary p. 3) the magnitude of error of cTnI levels (falsely elevated or falsely low) within a reasonably assumed change in temperature in a laboratory would not result in misclassification of patients from significant cardiac risk to no cardiac risk or vice versa.

3. Cardiac markers are typically ordered as one of several diagnostic tools used to aid in diagnosis of myocardial damage/infarction and should not be used in isolation. If erroneous patient results are generated for cTnI other diagnostic tools (including other cardiac markers, EKG) and clinical assessment should be available to override the erroneous results. However, erroneous results for cTnI could lead to less certainty about the actual diagnosis and therefore may be a confounding factor in the overall treatment decision process. Ultimately, however, the decision to treat should be made in light of total patient assessment.

C. **What Segment of the Population is Most at Risk? (e.g. Infants, Elderly, Pregnant Women, Critically Ill Patients, Immunocompromised, etc.)** The population most at risk is those patients with atypical and/or occult cardiac disease in whom clinical assessment and routine diagnostic tools are equivocal (i.e. non-ST-segment elevation acute coronary syndrome). Often woman will present with atypical cardiac symptoms.

D. **Does the Health Consequence Have Significant Public Health Impact Beyond Users (e.g. Spread of Serious Infection to Others)?** No

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Assess the Hazards Associated with Use of the Defective Product

Check All that Might Occur:

Population at Greatest Risk	Overall Population Using Device	
☒	☒	Life-threatening (death has or could occur)
☒	☒	Results in permanent impairment of body function or permanent damage to a body structure.
☒	☒	Necessitates medical or surgical intervention.
☒	☒	Temporary or reversible (without medical intervention).
☒	☒	Limited (transient, minor impairment or complaints).
☐	☐	No adverse health consequences.

Explanation:
The hazard associated with the use of the defective product(s) under this recall in both "at risk" populations, when taken in isolation, could lead to life threatening or permanent injury (using cTnI as the highest risk analyte). The probability of such hazard occurring is felt to be remote based on mitigating factors; Class II recall classification is recommended (as concluded by *ad hoc* HHE committee).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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IV. PROBABILITY

TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

Assess the Probability that Use of, or Exposure to, Product under Recall will Cause

A. Serious Adverse Health Consequences or Death

	Overall Population Using Device	Population at Greatest Risk
Reasonable Probability	☐	☐
Remote Probability	☒	☒
Not Likely	☐	☐

Explanation / Comments:
Ad hoc HHE committee was convened several times to discuss classification, in addition to consultation with "in-agency" cardiologist. After reviewing the CAPA investigation and all documentation it is felt that there is a remote probability of serious health consequences resulting from the device defect under consideration. It is the opinion of the majority of members of the *ad hoc* committee that the magnitude of error that would result with the highest risk analyte (cTnI) with reasonable change in laboratory temperature would not result in misclassification of patients from significant cardiac risk to no cardiac risk or vice versa.

B. Temporary or Medically Reversible Adverse Health Consequences

	Overall Population Using Device	Population at Greatest Risk
May Cause	☒	☒
Not Likely to Cause	☐	☐

Explanation / Comments: Temporary or medically reversible adverse health consequences may occur in both "at risk" patient populations.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Date: _August 30, 2011 Safety Officer: _Ian Pilcher

Signatures	Date	Printed Name, Title and Office
	08/30/2011	Jacqueline Wieneke, MD Medical Officer, CDRH\OIVD\DCTD
	08/30/2011	Ian Pilcher, CSO CDRH\OIVD\DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please share this information with your laboratory staff and retain this notification as part of your laboratory quality system documentation. Complete and return the enclosed response form within 10 days so we can be assured that you have received this important notification.

We understand the inconvenience that these steps may cause your laboratory. If you have any questions regarding this notification, please contact Technical Support at 1-800-854-3633 in the United States.

Thank you for your understanding, patience, and loyalty to Beckman Coulter.

Sincerely,

Nora Zerounian

Nora Zerounian
Group Manager, Corporate Quality and Regulatory Affairs

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Final DS w/ track changes

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System

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G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine ~~p~~Phosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator ~~secondary~~
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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2. Indication(s) for use:
The Access AccuTnI+3 ~~assay~~ Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 ~~assay~~ Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
For prescription use, for *in vitro* diagnostic use, not to be used for risk stratification

4. Special instrument requirements:
For use on the Access 2 Immunoassay System

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Comment [RAC2]: To be the same as Pathfast we should include it here

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I. Device Description:
The Access AccuTnI+3 Reagent packs contain:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrators ~~set~~ contains multi-point calibrators for use with the Access AccuTnI+3 ~~assay~~Reagent. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into

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the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of troponin test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrators
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrators; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Intended Use	~~An~~ *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma ~~to aid in the diagnosis of myocardial infarction.~~	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Indications For Use~~use~~	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma

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Comment [c4]: To be similar to pathfast, I suggest we put this is the differences table and just state the uses (one will have risk strat and one won't). Theme not have the risk stratification specifically called out separately.
Comment [PVC5R4]: Ruth, do you think this is acceptable or do you think I should remove Intended use altogether?
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61

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Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Instrument	Access 2 Immunoassay System with thermal algorithm capability	ADVIA Centaur System
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 ~~assay~~Reagent.	Intended to calibrate the ADVIA Centaur TnI-Ultra assay.

Differences		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

~~Similarities~~		
~~Item~~	~~Access 2 Immunoassay System~~	~~Predicate Device (k922823/A007)~~
~~Intended Use~~	~~For the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.~~	~~Same~~
~~Operating~~	~~Micro computer controlled, random and~~	~~Same~~

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Similarities		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Principle	continuous access	
Assay Type	Enzyme immunoassays	Same
Detection	Chemiluminescent	Same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems and computer/peripheral	Same

Differences		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Thermal Algorithm Capability	Present	Not present
Assay Protocol File (APF)	AccuTnI APF with addition of the thermal algorithm and "U" command (to improve mixing of the paramagnetic particle reagent); added result suppression when instrument internal case temperature is outside 18°C to 36°C	AccuTnI APF
Software	Version 3.3	Versions 2.4-3.2
Operating Temperature	18°C to 28°C ambient	18°C to 32°C ambient

K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

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63

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L. Test Principle:

The Access AccuTnI+3 ~~assay~~ Reagent is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The sponsor evaluated precision in several studies based on CLSI EP5-A2.

   The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally. ~~-~~A low spiked patient pool (lp), 3 commercial controls (c), and one high patient pool (hp). ~~Three commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample, and 1 pooled lithium heparin plasma sample~~ were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent ~~pack~~ lot.

   The third study was performed externally under ~~normal~~ existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on ~~one~~ 1 reagent lot and ~~one~~ 1 instrument.

   The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool ~~(sp)~~, 3 commercial controls ~~(c)~~, and one high patient pool ~~(hp)~~. These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

   The following data are representative of the results from the precision studies and are presented in the labeling:

64

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Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

Comment [c8]: Sp? Or is the typo above?

The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of 2 per run, 2 runs per shift and 2 shifts per day. ~~f X in X runs per day.~~ The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)
0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. ~~The first~~This study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study, ~~and~~ 3 instruments and ~~(how many reagent lots?).~~1 lot of reagent. The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1

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	5	8.348	3.8
3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate ~~(how many runs)~~ per run with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). Three sites ran a total of 20 runs, 1 site ran a total of 18 runs and 1 site ran a total of 40 runs. One instrument was used at each site. The results of ~~these studies~~the study ~~are~~ are summarized below:

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Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4
4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline

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utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions (from 18 to 28 °C) using lithium heparin plasma samples spiked with native cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of 8 replicates of each high and each low sample were analyzed and 4 replicates of each intermediate mixture of high and low ~~x replicates at each level~~ were analyzed with each reagent lot and instrument at each temperature. A ~~(for a~~ total of 12 independent analyses were performed~~)~~. The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The ~~sponsor claims that the~~ reportable range of the device is 0.02 ng/mL to ~~to the S5 calibrator (approximately~~ 100 ng/mL~~)~~.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

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d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent lots~~pucks~~, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low

67

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levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the different temperature conditions. The sponsor claims ~~that the~~an LoD o~~f is~~ 0.0~~1~~08 ng/mL.

To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions. ~~Three instruments and 2 reagent lots were used in this study.~~

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) ≤ ~~equal to~~ 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The ~~sponsor claims that the~~ reportable range of the device is 0.02 ng/mL to ~~the S5 calibrator (approximately~~ 100 ng/mL~~)~~.

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL samples) or ~~X~~ 10 (for the 0.05 ng/mL samples) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device. ~~(defined as less than 10% difference between the control sample result and the test sample result).~~

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%

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Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%
Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL, 13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%
Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 µg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 µg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL ~~troponin~~). Control and test samples were tested on ~~1~~ 6 instruments and ~~using X~~2 reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of ~~X~~10 for the low troponin samples (<0.02 ng/mL) and replicates of 5 for the high troponin samples (0.05 ng/mL). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that

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the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

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Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

f. Assay cut-off:
~~Refer to~~See section 4 "Clinical cut-off".

2. Comparison studies:

a. Method comparison:
Not applicable.

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from these~~is~~ analyses~~is~~):

Passing Bablok Regression by Concentration Ranges

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Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (-0 to 0)	~~R~~ r = 1.00
0.02 to 5	93	1 (0.98 to 1.00)	0.00 (0 to 0)	r= 0.99
0.02 to 0.04	75	1 (1.00 to 1.00)	0.00 (0 to 0)	r= 0.99

Clinical concordance analysis using 123 matched ~~clinical~~ samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

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Concordance at the 0.03 ng/mL cut-off

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

~~The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively.~~

An additional matrix comparison study was performed ~~3 times, once~~ at 3 different temperatures conditions (ranging from 18°C to 28°C) on 2 instruments using ~~one~~ 1 reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. The following are representative results (of singlicate measurements) of Passing-Bablok regression analysis and are presented in the labeling: ~~Results of Passing-Bablok regression analyses of singlicate measurements are provided below:~~

Range (ng/mL)	n	Slope (95% CI)	~~R~~r value	Intercept (95% CI)
0.02 - 71.76	97	1.03~~2~~ (1.00~~0.99~~ - 1.05~~4~~)	0.99	0.00 (-0.01 – 0.00)

3. Clinical studies:

a. *Clinical Sensitivity:*
A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline, 1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. Adjudicators were also blinded to site diagnoses. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

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Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	82.6~~3.3~~-	89.3 (1495/1675)	87.7~~8~~-90.7
≥1-3 h	96.0 (119/124)	90.8~~2.5~~-	89.4 (907/1014)	87.4~~6~~-91.3
≥3-6 h	94.9 (149/157)	90.2~~1.5~~-	86.7 (816/941)	84.4~~5~~-88.8~~9~~
≥6-9 h	90.7 (39/43)	~~82.0-~~	87.0 (214/246)	~~82.8-~~

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.12-	97.9 (1495/1527)	97.12-to
≥1-3 h	52.6 (119/226)	45.96.1-	99.5 (907/912)	98.79.0-
≥3-6 h	54.4 (149/274)	48.35-	99.0 (816/824)	98.14-99.67
≥6-9 h	54.9 (39/71)	42.73.4-	98.2 (214/218)	95.46.4-

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	86.27.3-	89.1 (885/993)	87.02-91.01
≥ 8 h	94.3 (150/159)	89.590.7-	86.8 (966/1113)	84.78-88.78

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.03-	98.4 (885/899)	97.46-99.23
≥ 8 h	50.5 (150/297)	44.78-	99.1 (966/975)	98.35-99.67

Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.18-	84.3 (1412/1675)	82.56-86.0
≥1-3 h	98.4 (122/124)	96.2-	85.5 (867/1014)	83.23-87.67
≥3-6 h	98.1 (154/157)	95.9-	81.0 (762/941)	78.5-
≥6-9 h	93.0 (40/43)	85.4-	76.4 (188/246)	71.1-

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.56-	98.6 (1412/1432)	97.98.0-
≥1-3 h	45.4 (122/269)	39.34-	99.8 (867/869)	99.25-100
≥3-6 h	46.2 (154/333)	40.89-	99.6 (762/765)	98.99.2-
≥6-9 h	40.8 (40/98)	31.01-	98.4 (188/191)	95.56.7-

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	92.3-	83.2 (826/993)	80.79-85.5
≥ 8 h	96.9 (154/159)	92.84.1-	81.7 (909/1113)	79.34-83.9

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.23-	99.3 (826/832)	98.47-99.79
≥ 8 h	43.0 (154/358)	37.89-	99.5 (909/914)	98.79.5-

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) ~~of~~ <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.9-	93.9 (1572/1675)	92.7-
≥1-3 h	89.5 (111/124)	84.1-	93.5 (948/1014)	92.0-
≥3-6 h	87.3 (137/157)	82.0-	93.0 (875/941)	91.4-
≥6-9 h	90.7 (39/43)	82.0-	93.1 (229/246)	89.9-

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	59.760.0-	96.4 (1572/1630)	95.45-97.3
≥1-3 h	62.7 (111/177)	55.16-	98.6 (948/961)	97.79-99.34
≥3-6 h	67.5 (137/203)	60.61.0-	97.8 (875/895)	96.68-98.67
≥6-9 h	69.6 (39/56)	55.97.6-	98.3 (229/233)	95.76.6-

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	80.179.1-	93.6 (929/993)	91.8-
≥ 8 h	88.1 (140/159)	82.03.0-	92.7 (1032/1113)	91.02-94.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.04-75.1	97.5 (929/953)	96.35-98.45
≥ 8 h	63.3 (140/221)	56.657.0-	98.2 (1032/1051)	97.24-

b. *Clinical specificity:*
See clinical specificity information above in 3a.

c. *Other clinical supportive data (when a. and b. are not applicable):*
Not applicable

4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance

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information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) ~~of~~ <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included in the reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:

1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
Yes __X__ or No ____

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Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X__

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2. Software:
FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
Yes __X__ or No _____

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3. Specimen Identification:
Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
Instructions on sample handling are~~is~~ provided in the reagent labeling.

5. Calibration:
An active calibration curve is required for all tests. For the Access AccuTnI+3 Reagent ~~Access AccuTnI assay~~, calibration is required every 56 days.

76

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6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

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P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies to demonstrate the impact of ambient temperature differences on the test result. Three of these (3 studies focused on low dose (LD) troponin concentrations around the cut-offs (0.02 to —0.4. ng/mL for study 1; 0.02 to 0.6 ng/mL for studies 2 and 3). Study 4 evaluated the and 1 study evaluating the full reportable range (FR) of the device (FR0.03 to 94 ng/mL) and regression analysis of low dose (LD) samples with troponin concentrations around the cut-off (0.03 to 0.4 ng/mL) was also performed. In total, of the assay) to demonstrate the impact of ambient temperature differences on the test result. Seven hundred fifty one751 (751) lithium heparin plasma samples were tested in total at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperature conditionss. The sponsor analyzed the same samples run under different temperature conditionsperformed using Passing-Bablok regression analyseis of singlicate test results. The results of the 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

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Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98
	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2 LD	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3 LD	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00

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	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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S. Other Supportive Device and Instrument Information:

Additional Linearity ~~data~~Study: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For ~~the~~ 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

Clinical matrix comparison: The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively. The sponsor concluded that this analysis demonstrated equivalent clinical performance between the matrices.

Sponsor's postmarket monitoring plan and proposed corrective action plan: This 510(k) is the result of a warning letter and 2 major recalls (please refer to the copies of the warning letter dated June 10, 2010, RES 54729, RES 58719, Beckman's reply to the warning letter dated July 14, 2010 and a copy of the urgent product correction action for the Access AccuTnI update dated June 18, 2010. All of these are enclosed). The device includes a fix validated with one set of conflicting data (see review memo documentation below). To ensure patient safety, the sponsor will implement the following plan at commercialization (please refer to a copy of the sponsors' "Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)" which is enclosed, for the sponsor's complete plan).

The sponsor has established an AccuTnI+3 Early Response Team (ERT), to monitor the performance of the device for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the device, including product performance.

If US annual discrete events on the Access2 instrument – 1 to 4 (Low incidence rate)
1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)
1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility

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3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)
1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

T. Administrative Information:

1. *Applicant contact information:*
   a. *Name of applicant:* Beckman Coulter Inc.
   b. *Mailing address:* 1000 Lake Hazeltine Drive, Chaska, MN 55318
   c. *Phone #:* (952)368-7858
   d. *Fax #:* (952)368-7610
   e. *E-mail address (optional):* ksoetter@beckman.com
   f. *Contact:* Kerrie S. Oetter

2. Review documentation:
   ~~2.~~ As described above in Section S, "Sponsor's postmarket monitoring plan and proposed corrective action plan", this 510(k) is the result of a warning letter and 2 major recalls and includes a fix that the sponsor is implementing (a thermal algorithm) to correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results. This algorithm is validated with one set of conflicting data. Specifically, when FDA analyzed the results from the "Thermal Sensitivity – Impact on Low Dose Concordance/Agreement study" that the sponsor provided in support of the algorithm, the estimates of the intercepts in these regressions was always 0, but, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 (95% CI of 1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 (95% CI 1.26, 1.40). In FDA's June 20, 2012 request for additional information letter, the agency expressed concern that the corrective algorithm may not resolve the thermal sensitivity from ambient temperature (please refer to the June 20, 2012 review memo). In response, the sponsor hypothesized that the anomalous results from

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the study were due to improper sample handling (that resulted in samples that were not thermally sensitive and thereby improperly corrected by application of the thermal algorithm), however, they did not identify a root cause for the unacceptable performance of the device in the temperature concordance study provided in the submission (please refer to the sponsor's December 14, 2012 response). The sponsor provided additional thermal sensitivity agreement studies in support of the algorithm (please refer to Section P of the decision summary). During the February 4, 2013 meeting with the sponsor, FDA requested an approach to make sure that the corrective algorithm is safe and effective and if it fails in the intended use setting, that the sponsor have a mechanism in place to ensure patient safety (please refer to the meeting minutes for the February 4, 2013 in-person meeting with the sponsor). On June 13, 2013, the sponsor provided their proactive approach (please refer to Section S, "Sponsor's postmarket monitoring plan and proposed corrective action plan").

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3. Substantial Equivalence Discussion:

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	Yes	No	
1. Same Indication Statement?	~~X~~	X	If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?		X	If YES = Stop NSE
3. Same Technological Characteristics?	X		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	X		If NO = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: SE~~CS~~

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

Field Code Changed

a. ~~a.~~ *Explain how the new indication differs from the predicate device's indication:*

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The predicate device includes a claim for risk stratification, the indications for use for this device does not include this claim.

b. ~~b.~~ *Explain why there is or is not a new effect or safety or effectiveness issue:* By excluding the indication for risk stratification, there is no new safety or effectiveness issue since other clinical information can be used to assess patient risk.

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:* Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed *in vitro* diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:* See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template sections M, P and S ~~—performance characteristics above~~ for more information.

U. Reviewer Name and Signature:

Paula Caposino, Ph.D.
CDRH/OIR~~VD~~/DCTD

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Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

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Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Ruth A. Chesler-S

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k) k121214

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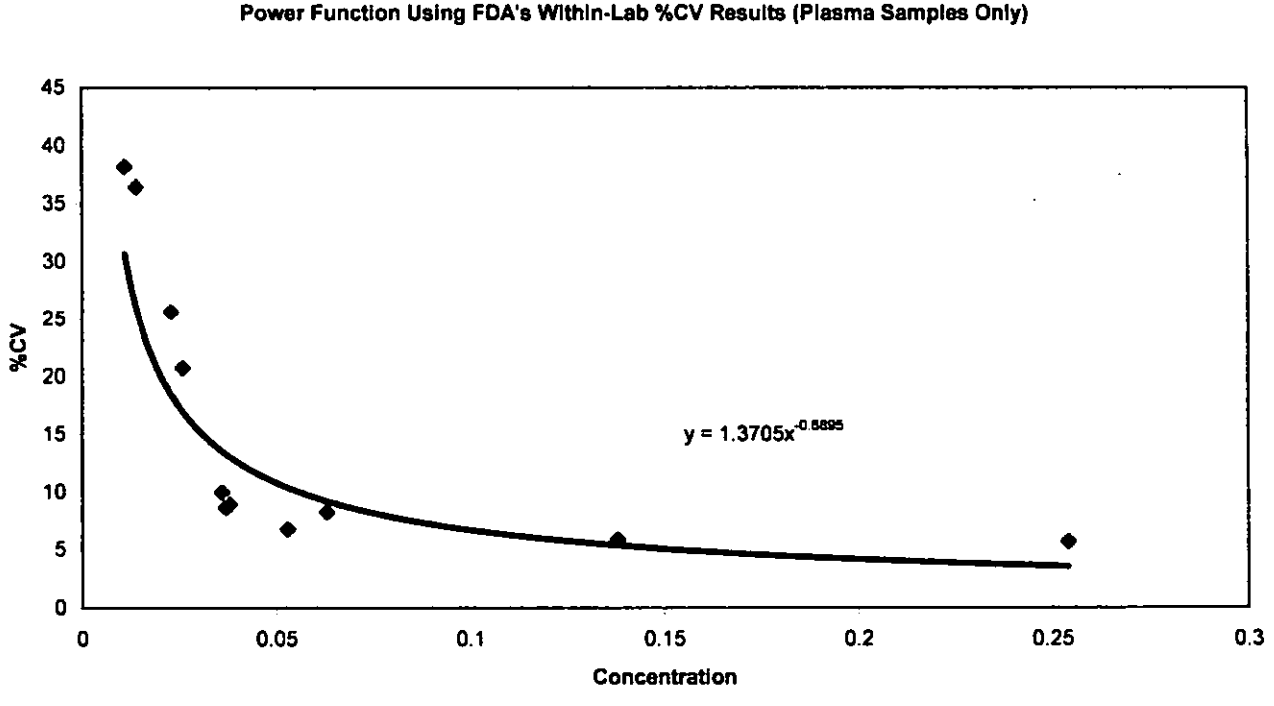
To: The record of k121214
From: Arkendra De, Statistician, OSB/DBS/DDB
Date: June 13, 2013
FDA used the Excel spreadsheet data [of the sponsor's LoQ studies] from the sponsor (plasma samples only) to calculate the mean and %CV within-lab for each of the 11 samples, combining across temperature, instrument, run, and day. Below are FDA's results].

Sample ID	Mean	Within-Lab Standard Deviation	%CV
1	0.011	0.0042	38.181818
2	0.014	0.0051	36.428571
3	0.023	0.0059	25.652174
4	0.026	0.0054	20.769231
5	0.037	0.0032	8.648649
6	0.038	0.0034	8.947368
7	0.053	0.0036	6.792453
8	0.063	0.0052	8.253968
9	0.138	0.0081	5.869565
10	0.254	0.0144	5.669291
11	0.036	0.0036	10.000000

Using the above table, FDA constructed a precision profile analysis, following CLSI EP 17-A2. The below graph depicts the statistical model using the precision profile approach.



Using the equation shown in the above chart, a concentration of 0.02 yields a %CV of 20.3%, very close to the sponsor's goal of 20% CV.

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(b)(4)

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Friday, June 14, 2013 3:59 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Clinical Performance Summary table
Attachments: Clinical Performance Data for Exact 95.pdf

Importance: High

Dear Paula,

Attached is the Clinical Performance Data you requested. Please let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, June 14, 2013 1:31 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: Clinical Performance Summary table

OK. Let me know as soon as possible when you will have those ready.
Thanks.
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Friday, June 14, 2013 2:29 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Clinical Performance Summary table

Dear Paula,

The originator that generated the tables is not here today, so we are in the process of locating the original files. We believe we can response within two hours.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, June 14, 2013 11:58 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: FW: Clinical Performance Summary table
Importance: High

Dear Kerrie,
I realized I sent this to you to your personal email.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Please see my request below and please note that we are not asking for any changes to IFU, we just need to have the data on file.
Thanks,
'aula

Do you have an idea when I may be able to get this information?
Paula

From: Caposino, Paula
Sent: Friday, June 14, 2013 11:50 AM
To: Kerrie Oetter (koetter@live.com)
Cc: Cundy, Scott T (STCundy@beckman.com)
Subject: Clinical Performance Summary table
Importance: High

Dear Scott and Kerrie,

One last hiccup. This is the clinical performance data that I have and it seems to have Wald 95%CI and not the Exact 95% CI that are in the label.
Can you please get me all of the data with the Exact 95% CIs? Can you please make sure that the CI are not rounded up (i.e., 98.5 and not 99%).

Can you please get this to me ASAP

Thanks,

Paula

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Clinical Performance Data for Exact 95% CI

PPV and NPV for Serial Time Intervals after System Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43.2 – 54.3	99	826/832	98.4 – 99.7
	≥ 8 hours	43	154/358	37.8 – 48.3	100	909/914	98.7 – 99.8
0.03	< 8 hours	58	151/259	52.0 – 64.4	98	885/899	97.4 – 99.2
	≥ 8 hours	51	150/297	44.7 – 56.3	99	966/975	98.3 – 99.6
0.04	< 8 hours	69	141/205	62.0 – 75.1	98	929/953	96.3 – 98.4
	≥ 8 hours	63	140/221	56.6 – 69.7	98	1032/1051	97.2 – 98.9

PPV and NPV for Serial Time Intervals after Admission to the Emergency Room

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	42.5 – 51.5	99	1412/1432	97.9 – 99.1
	≥ 1 to 3	45	122/269	39.3 – 51.5*	100	867/869	99.2 – 100.0
	≥ 3 to 6	46	154/333	40.8 – 51.8	100	762/765	98.9 – 99.9
	≥ 6 to 9	41	40/98	31.0 – 51.2	98	188/191	95.5 – 99.7
0.03	Baseline	55	221/401	50.1 – 60.1	98	1495/1527	97.1 – 98.6
	≥ 1 to 3	53	119/226	45.9 – 59.3	100	907/912	98.7 – 99.8
	≥ 3 to 6	54	149/274	48.3 – 60.4	99	816/824	98.1 – 99.6
	≥ 6 to 9	55	39/71	42.7 – 66.8	98	214/218	95.4 – 99.5
0.04	Baseline	65	195/298	59.7 – 70.8	96	1572/1630	95.4 – 97.3
	≥ 1 to 3	63	111/177	55.1 – 69.9	99	948/961	97.7 – 99.3
	≥ 3 to 6	68	137/203	60.6 – 73.9	98	875/895	96.6 – 98.6
	≥ 6 to 9	70	39/56	55.9 – 81.2	98	229/233	95.7 – 99.5

*51.5– actual value is .5148 will round to 51% in IFU

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Diagnostic Sensitivity & Specificity for Serial Time after System Onset

Tnl cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92.3 – 98.7	83	826/993	80.7 – 85.5*
	≥ 8 hours	97	154/159	92.8 – 99.0	82	909/1113	79.3 – 83.9
0.03	< 8 hours	92	151/165	86.2 – 95.3	89	885/993	87.0 – 91.0
	≥ 8 hours	94	150/159	89.5 – 97.4	87	966/1113	84.7 – 88.7
0.04	< 8 hours	86	141/165	79.1 – 90.5**	94	929/993	91.8 – 95.0
	≥ 8 hours	88	140/159	82.0 – 92.7	93	1032/1113	91.0 – 94.2

*85.5 - actual value is .8546 will round to 85% in IFU

**90.5 – actual value is .9045 will round to 90% in IFU

Diagnostic Sensitivity & Specificity for Serial Time after Admission to Emergency Department

Tnl cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88.1 – 95.1	84	1412/1675	82.5 – 86.0
	≥ 1 to 3	98	122/124	94.3 – 99.8	86	867/1014	83.2 – 87.6
	≥ 3 to 6	98	154/157	94.5 – 99.6	81	762/941	78.3 – 83.4
	≥ 6 to 9	93	40/43	80.9 – 98.5	76	188/246	70.6 – 81.6
0.03	Baseline	87	221/253	82.6 – 91.2	89	1495/1675	87.7 – 90.7
	≥ 1 to 3	96	119/124	90.8 – 98.7	89	907/1014	87.4 – 91.3
	≥ 3 to 6	95	149/157	90.2 – 97.8	87	816/941	84.4 – 88.8
	≥ 6 to 9	91	39/43	77.9 – 97.4	87	214/246	82.1 – 90.9
0.04	Baseline	77	195/253	71.4 – 82.1	94	1572/1675	92.6 – 95.0
	≥ 1 to 3	90	111/124	82.7 – 94.3	94	948/1014	91.8 – 94.9
	≥ 3 to 6	87	137/157	81.0 – 92.0	93	875/941	91.2 – 94.5
	≥ 6 to 9	91	39/43	77.9 – 97.4	93	229/246	89.2 – 95.9

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Caposino, Paula

From: Chesler, Ruth A
Sent: Friday, June 14, 2013 11:06 AM
To: Caposino, Paula
Subject: FW: k121214 Decision Summary (2).doc
Attachments: k121214 Decision Summary (2).doc

Paula – I just had some small edits –

Ruth

From: Caposino, Paula
Sent: Thursday, June 13, 2013 3:48 PM
To: Chesler, Ruth A
Cc: Lias, Courtney H
Subject: k121214 Decision Summary (2).doc

Here is the DS. I may still have to tweak some of the 95%CI confidence intervals in the clinical performance since the sponsor is making sure that they are all correct (these will be very minor tweaks). I have added all of the little details that were missing and have added a discussion of the sponsor's postmarket monitoring plan in the non-public section. Let me know if this is ok.
Thanks,
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System

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G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine pPhosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator ~~secondary~~
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

92

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2. Indication(s) for use:
The Access AccuTnI+3 ~~assay~~ Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 ~~assay~~ Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
For prescription use, for *in vitro* diagnostic use, not to be used for risk stratification

4. Special instrument requirements:
For use on the Access 2 Immunoassay System

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Comment [RAC2]: To be the same as Pathfast we should include it here

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I. Device Description:
The Access AccuTnI+3 Reagent packs contain:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrators ~~set~~ contains multi-point calibrators for use with the Access AccuTnI+3 ~~assay~~Reagent. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into

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the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrators
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrators; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Intended Use	~~An~~ *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma. ~~to aid in the diagnosis of myocardial infarction.~~	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Indications For Use~~use~~	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma
Instrument	Access 2 Immunoassay System with thermal algorithm capability	PATHFAST Analyzer

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Comment [c4]: To be similar to pathfast, I suggest we put this is the differences table and just state the uses (one will have risk strat and one won't). There not have the risk stratification specifically called out separately.
Comment [PVC5R4]: Ruth, do you think this is acceptable or do you think I should remove Intended use altogether?
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94

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Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibratorss	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 ~~assay~~Reagent~~.~~	Intended to calibrate the TnI-Ultra assay.

Differences		
Item	Access AccuTnI+3 Calibratorss	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

~~Similarities~~		
~~Item~~	~~Access 2 Immunoassay System~~	~~Predicate Device (k922823/A007)~~
~~Intended Use~~	~~For the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.~~	~~Same~~
~~Operating Principle~~	~~Micro computer controlled, random and continuous access~~	~~Same~~
~~Assay Type~~	~~Enzyme immunoassays~~	~~Same~~

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Comment [c7]: Instrument? I prefer we put the instrument and assay reagents together in this description since the instrument doesn't need clearance on its own. Only the parameters here relevant to this system need to be included
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Similarities		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Detection	Chemiluminescent	Same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems and computer/peripheral	Same

Differences		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Thermal Algorithm Capability	Present	Not present
Assay Protocol File (APF)	AccuTnI APF with addition of the thermal algorithm and "U" command (to improve mixing of the paramagnetic particle reagent); added result suppression when instrument internal case temperature is outside 18°C to 36°C	AccuTnI APF
Software	Version 3.3	Versions 2.1-3.2
Operating Temperature	18°C to 28°C ambient	18°C to 32°C ambient

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Comment [c7]: Instrument? I prefer we put the instrument and assay reagents together in this description since the instrument doesn't need clearance on its own. Only the parameters here relevant to this system need to be included.

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K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

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L. Test Principle:

The Access AccuTnI+3 ~~assay~~ Reagent is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The sponsor evaluated precision in several studies based on CLSI EP5-A2.

   The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally Three commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample, and 1 pooled lithium heparin plasma sample were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent pack lot.

   The third study was performed externally under ~~normal~~ existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on one reagent lot and one instrument.

   The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool (lsp), 3 commercial controls (c), and one high patient pool (hp). These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

   The following data are representative of the results from the precision studies and are presented in the labeling:

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Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

Comment [c8]: Sp? Or is the typo above?

The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of 2 per run, 2 runs per shift and 2 shifts per day. ~~f X in X runs per day.~~ The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)
0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. The first study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study ~~and~~ 3 instruments and ~~(how many reagent lots?).~~ 1 lot of reagent. The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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	5	8.348	3.8
3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate ~~(how many runs)~~ per run with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). Three sites ran a total of 20 runs, 1 site ran a total of 18 runs and 1 site ran a total of 40 runs. One instrument was used at each site. The results of these studies are summarized below:

Comment [PVC9]: If you prefer Ruth, I can put in the tables with the full data instead of the range.

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Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4
4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions

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(from 18 to 28 °C) using lithium heparin plasma samples spiked with native cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of 8 replicates of each high and each low sample were analyzed and 4 replicates of each intermediate mixture of high and low ~~x replicates at each level~~ were analyzed with each reagent lot and instrument at each temperature (for a total of 12 independent analyses). The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

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d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent packs, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the

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different temperature conditions. The sponsor claims ~~that the~~an LoD of~~is~~ 0.008 ng/mL.

To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions. Three instruments and 2 reagent lots were used in this study.

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) equal to 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL) or ~~X~~ 10 (for the 0.05 ng/mL) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device (defined as less than 10% difference between the control sample result and the test sample result).

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%
Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL, 13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%
Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 µg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 µg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL ~~troponin~~). Control and test samples were tested on ~~1~~ 6 instruments and ~~using X~~ 2 reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of ~~X~~10 for the low troponin samples (<0.02 ng/mL) and replicates of 5 for the high troponin samples (0.05 ng/mL). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

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Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

f. Assay cut-off:
Refer to section 4 "Clinical cut-off".

2. Comparison studies:

a. Method comparison:
Not applicable.

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from these~~is~~ analyse~~is~~):

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Passing Bablok Regression by Concentration Ranges

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (-0 to 0)	~~R~~ r = 1.00
0.02 to 5	93	1 (0.98 to 1.00)	0.00 (0 to 0)	r= 0.99
0.02 to 0.04	75	1 (1.00 to 1.00)	0.00 (0 to 0)	r= 0.99

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Clinical concordance analysis using 123 matched clinical samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

~~The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively.~~

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An additional study was performed 3 times, once at 3 different temperatures conditions (ranging from 18 to 28°C) on 2 instruments using one reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. Results of Passing-Bablok regression analyses of singlicate measurements are provided below:

Temp	Range (ng/mL)	Slope (95% CI)	R value	Intercept (95% CI)	n
18°C	0.02 - 77.96	1.03 (1.01 - 1.06)	0.99	-0.01 (-0.01 – 0.00)	97
23°C	0.02 - 71.76	1.02 (0.99 - 1.04)	0.99	0.00 (-0.01 – 0.00)	97
28°C	0.02 - 66.76	1.04 (1.01 - 1.06)	0.99	0.00 (-0.01 – 0.00)	97

3. Clinical studies:

   a. *Clinical Sensitivity:*
   A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline,

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1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	83.3-91.4	89.3 (1495/1675)	87.8-90.7
1-3 h	96.0 (119/124)	92.5-99.4	89.4 (907/1014)	87.6-91.3
3-6 h	94.9 (149/157)	91.5-98.3	86.7 (816/941)	84.5-88.9
6-9 h	90.7 (39/43)	82.0-99.4	87.0 (214/246)	82.8-91.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.2-60.0	97.9 (1495/1527)	97.2 to 98.6
1-3 h	52.6 (119/226)	46.1-59.2	99.5 (907/912)	99.0-99.9
3-6 h	54.4 (149/274)	48.5-60.3	99.0 (816/824)	98.4-99.7
6-9 h	54.9 (39/71)	43.4-66.5	98.2 (214/218)	96.4-99.9

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Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	87.3-95.8	89.1 (885/993)	87.2-91.1
≥ 8 h	94.3 (150/159)	90.7-97.9	86.8 (966/1113)	84.8-88.8

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.3-64.3	98.4 (885/899)	97.6-99.3
≥ 8 h	50.5 (150/297)	44.8-56.2	99.1 (966/975)	98.5-99.7

Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.8-95.4	84.3 (1412/1675)	82.6-86.0
1-3 h	98.4 (122/124)	96.2-100	85.5 (867/1014)	83.3-87.7
3-6 h	98.1 (154/157)	95.9-100	81.0 (762/941)	78.5-83.5
6-9 h	93.0 (40/43)	85.4-100	76.4 (188/246)	71.1-81.7

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.6-51.4	98.6 (1412/1432)	98.0-99.2
1-3 h	45.4 (122/269)	39.4-51.3	99.8 (867/869)	99.5-100
3-6 h	46.2 (154/333)	40.9-51.6	99.6 (762/765)	99.2-100
6-9 h	40.8 (40/98)	31.1-50.5	98.4 (188/191)	96.7-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	93.5-99.2	83.2 (826/993)	80.9-85.5
≥ 8 h	96.9 (154/159)	94.1-99.6	81.7 (909/1113)	79.4-83.9

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.3-54.2	99.3 (826/832)	98.7-99.9
≥ 8 h	43.0 (154/358)	37.9-48.1	99.5 (909/914)	99.5-99.9

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) of <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.9-82.3	93.9 (1572/1675)	92.7-95.0
1-3 h	89.5 (111/124)	84.1-94.9	93.5 (948/1014)	92.0-95.0
3-6 h	87.3 (137/157)	82.0-92.5	93.0 (875/941)	91.4-94.6
6-9 h	90.7 (39/43)	82.0-99.4	93.1 (229/246)	89.9-96.3

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	60.0-70.8	96.4 (1572/1630)	95.5-97.3
1-3 h	62.7 (111/177)	55.6-69.8	98.6 (948/961)	97.9-99.4
3-6 h	67.5 (137/203)	61.0-73.9	97.8 (875/895)	96.8-98.7
6-9 h	69.6 (39/56)	57.6-81.7	98.3 (229/233)	96.6-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	80.1-90.8	93.6 (929/993)	92.0-95.1
≥ 8 h	88.1 (140/159)	83.0-93.1	92.7 (1032/1113)	91.2-94.2

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.4-75.1	97.5 (929/953)	96.5-98.5
≥ 8 h	63.3 (140/221)	57.0-69.7	98.2 (1032/1051)	97.4-99.0

b. *Clinical specificity:*
See clinical specificity information above in 3a.

c. *Other clinical supportive data (when a. and b. are not applicable):*

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4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) of <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:
1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
Yes __X__ or No ____

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Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X__

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2. Software:
   FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
   Yes __X__ or No _____

3. Specimen Identification:
   Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
   Instruction on sample handling is provided in the reagent labeling.

5. Calibration:
   An active calibration curve is required for all tests. For the Access AccuTnI Reagent~~assay~~, calibration is required every 56 days.

6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

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P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies to demonstrate the impact of ambient temperature differences on the test result. Three of these ~~(3~~ studies focused on ~~low dose (LD)~~ troponin concentrations around the cut-offs ~~(~~0.02 to ~~—~~0.4~~.~~ ng/mL for study 1; 0.02 to 0.6 ng/mL for studies 2 and 3). Study 4 evaluated the ~~and 1 study evaluating the~~ full reportable range (FR) of the device (~~FR~~0.03 to 94 ng/mL) and regression analysis of low dose (LD) samples with troponin concentrations around the cut-off (0.03 to 0.4 ng/mL) was also performed. In total, ~~of the assay) to demonstrate the impact of ambient temperature differences on the test result. Seven hundred fifty one~~751 ~~(751)~~ lithium heparin plasma samples were tested ~~in total~~ at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperature conditions~~s~~. The sponsor analyzed the same samples run under different temperature conditions using Passing-Bablok regression analysis of singlicate test results: The results of 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

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Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98

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	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2 ~~LD~~	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3 ~~LD~~	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00
	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

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S. Other Supportive Device and Instrument Information:

Additional Linearity ~~data~~Study: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For the 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

Clinical matrix comparison: The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively. The sponsor concluded that this analysis demonstrated equivalent clinical performance between the matrices.

Sponsor's postmarket monitoring plan: This 510(k) is the result of a warning letter and 2 recalls (please refer to the copies of the warning letter dated June 10, 2010, RES 54729 and RES 58719 included in the file of this submission) and includes a fix validated with one set of conflicting data (see review memo documentation below). To ensure patient safety, the sponsor will implement the following plan at commercialization (please refer to sponsor's response to FDA's June 10, 2013 Request for Additional Information letter for complete plan):

The sponsor has established an AccuTnI+3 Early Response Team (ERT), to monitor the performance of the device for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the device, including product performance.

If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)
1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)
1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation

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Comment [c16]: I suggest we put this in the non-public section.

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6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)
1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

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T. Administrative Information:

1. *Applicant contact information:*
   - *a. Name of applicant:* Beckman Coulter Inc.
   - *b. Mailing address:* 1000 Lake Hazeltine Drive, Chaska, MN 55318
   - *c. Phone #:* (952)368-7858
   - *d. Fax #:* (952)368-7610
   - *e. E-mail address (optional):* ksoetter@beckman.com
   - *f. Contact:* Kerrie S. Oetter

2. Review documentation:

~~2.~~ As described above in Section S, "postmarket monitoring", this 510(k) is the result of a warning letter and 2 recalls and includes a fix that the sponsor is implementing (a thermal algorithm) to correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results. This algorithm is validated with one set of conflicting data. Specifically, when FDA analyzed the results from the "Thermal Sensitivity - Impact on Low Dose Concordance/Agreement study" that the sponsor provided in support of the algorithm, the estimates of the intercepts in these regressions was always 0, but, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 (95% CI of 1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 (95% CI 1.26, 1.40). In FDA's June 20, 2012 request for additional information letter, the agency expressed concern that the corrective algorithm may not resolve the thermal sensitivity from ambient temperature (please refer to the June 20, 2012 review memo). In response, the sponsor hypothesized that the anomalous results from the study were due to improper sample handling (that resulted in samples that were not thermally sensitive and thereby improperly corrected by application of the thermal algorithm), however, they did not identify

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112

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a root cause for the unacceptable performance of the device in the temperature concordance study provided in the submission (please refer to the December 14, 2012 response). The sponsor provided additional thermal sensitivity agreement studies in support of the algorithm (please refer to Section P of the decision summary). During the February 4, 2013 meeting with the sponsor, FDA requested an approach to make sure that the corrective algorithm is safe and effective and if it fails in the intended use setting, that the sponsor have a mechanism in place to ensure patient safety (please refer to the meeting minutes for the February 4, 2013 in-person meeting with the sponsor). On June 13, 2013, the sponsor provided their proactive approach (please refer to Section S, postmarket monitoring).

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3. Substantial Equivalence Discussion:

	Yes	No	
1. Same Indication Statement?	~~X~~	X	If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?		X	If YES = Stop NSE
3. Same Technological Characteristics?	X		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	X		If NO = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: CS

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

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a. ~~a.~~ *Explain how the new indication differs from the predicate device's indication:*
The predicate device includes a claim for risk stratification, the indications for use for this device does not include this claim.

b. ~~b.~~ *Explain why there is or is not a new effect or safety or effectiveness issue:*

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By excluding the indication for risk stratification, there is no new safety or effectiveness issue since other clinical information can be used to assess patient risk.

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:*
Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed *in vitro* diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:*
See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template sections M, P and S ~~—performance characteristics above~~ for more information.

U. Reviewer Name and Signature:

Paula Caposino, Ph.D.
CDRH/OIR~~VD~~/DCTD

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Friday, June 14, 2013 11:17 AM
To: Caposino, Paula; Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx
Attachments: AccuTnI+3 Access 2 IFU B16315A 2.pdf

Importance: High

Dear Paula,

BEC is brand-neutral regarding QC materials, and cannot publish recommendations regarding specific brands of commercial quality control materials without legal agreement with the manufacturers. We have added a statement, similar to that in the Limitations of the Procedure into the Quality Control section of the IFU regarding the development of the algorithm using the thermal profile of native troponin.

Please see the revised IFU which is attached.

Regards,
Kerrie Oetter

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, June 14, 2013 8:35 AM
To: Cundy, Scott T
Cc: Oetter, Kerrie S
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Thanks

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Friday, June 14, 2013 8:46 AM
To: Caposino, Paula
Cc: Oetter, Kerrie S
Subject: Re: AccuTnI+3 Access 2 IFU word version (2).docx

Hello Paula,

We'll look into this and respond as quickly as possible.

Thank you,
Scott

Sent from my iPhone

On Jun 14, 2013, at 7:15 AM, "Caposino, Paula" <Paula.Caposino@fda.hhs.gov> wrote:

Dear Scott and Kerrie,

115

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Thank you very much for the information and changes to the instructions for use. One more question/suggestion:

If there are commercially available QC materials that may not be compatible with your device because they do not have the same thermal profile as native cardiac troponin I, we recommend that you somehow incorporate this information in the QC section of your labeling. Let me know.

Thanks a lot,
Paula

Please be advised that this email may contain confidential information. If you are not the intended recipient, please notify us by email by replying to the sender and delete this message. The sender disclaims that the content of this email constitutes an offer to enter into, or the acceptance of, any agreement; provided that the foregoing does not invalidate the binding effect of any digital or other electronic reproduction of a manual signature that is included in any attachment.

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty-five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance of the quality control material. The thermal profile of native human cardiac troponin I was used in development of this assay. Quality control materials containing troponin I not from this source

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(e.g. recombinant antigens) may behave differently. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects

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were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

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To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 –86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04

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ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to

125

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determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[34] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL

126

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Substance	Highest Concentration Added
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol

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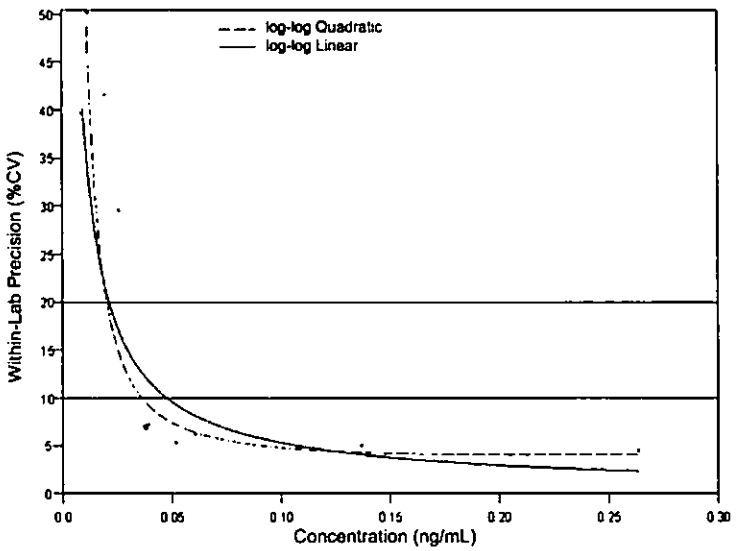
based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

Limit of Quantitation (imprecision estimate)



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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32 Approved Guideline – Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach, EP6-A. April 2003. Clinical and Laboratory Standards Institute.
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34 Approved Guideline – Interference Testing in Clinical Chemistry, EP7-A2. November 2005. Clinical and Laboratory Standards Institute.

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Beckman Coulter, Inc.
250 S. Kraemer Blvd.
Brea, CA 92821 U.S.A.

Printed in U.S.A.
Made in U.S.A.
Issued April 2013

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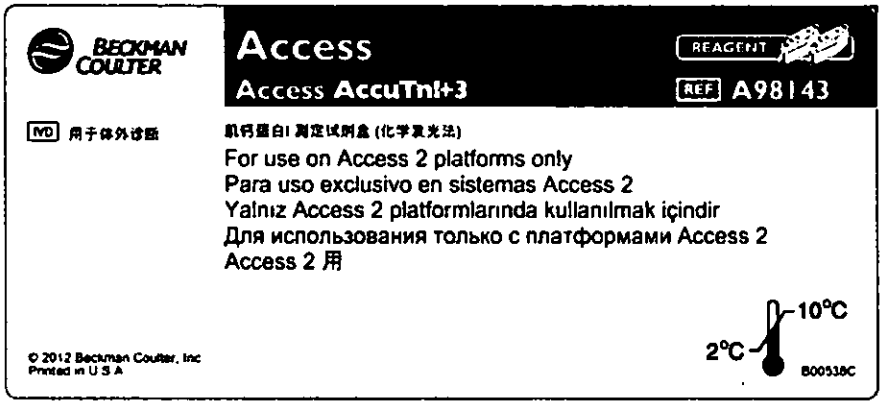
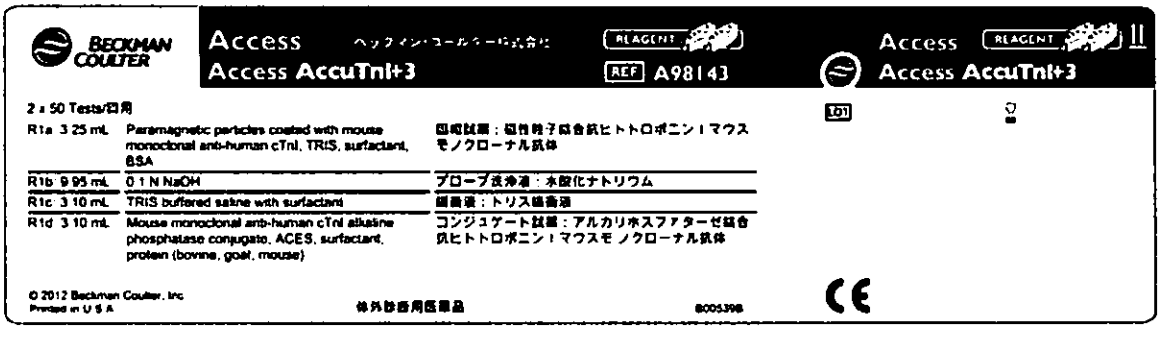
Access Reagent labels:





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Access

Access AccuTnI+3

REAGENT

REF A98143

2 reagent packs R1, for the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.

2 envases de reactivos R1, para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.

Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini nicelıksel olarak tespit etmek için 2 reaktif paketi R1.

2 комплекта реагентов R1 для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.

クラスIII生化学・免疫・内分泌検査用シリーズ　トロポニンキット　/　アクセス AccuTnI 試薬パック

Xi ≥ 0.0375 – < 1.5% ProClin™ 300
R 43 S 26-37

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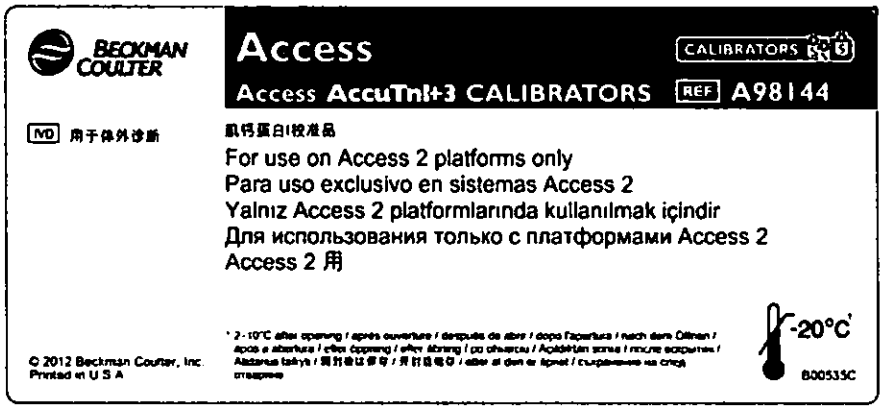

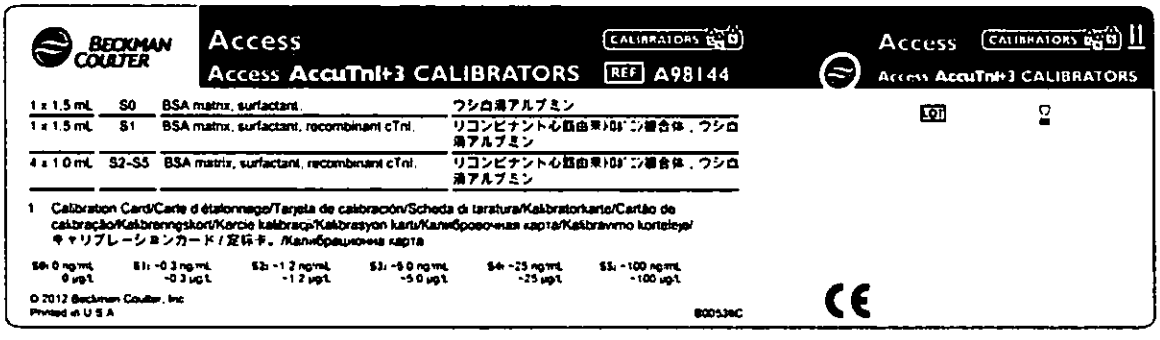

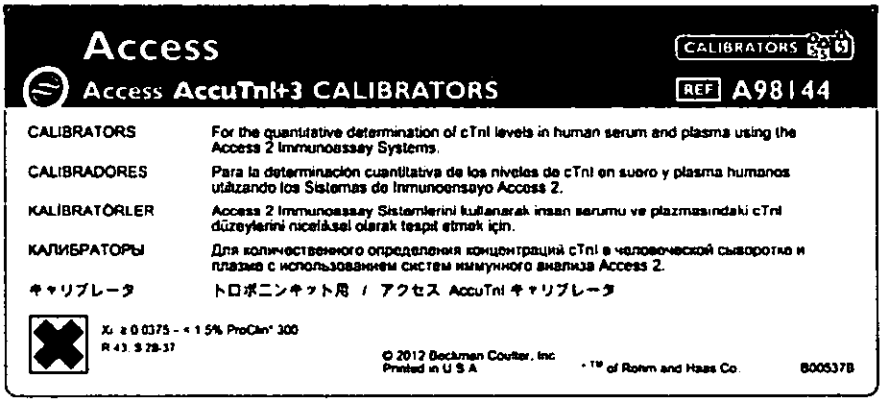

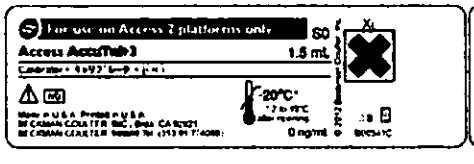

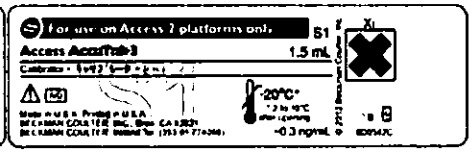

135

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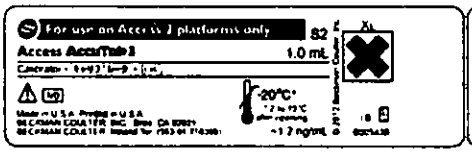
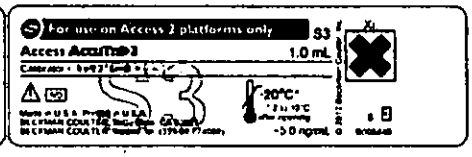
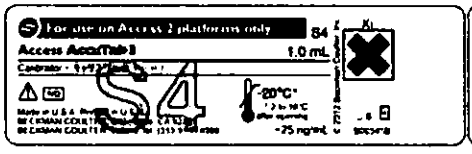
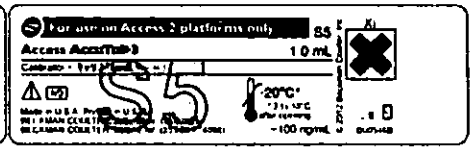
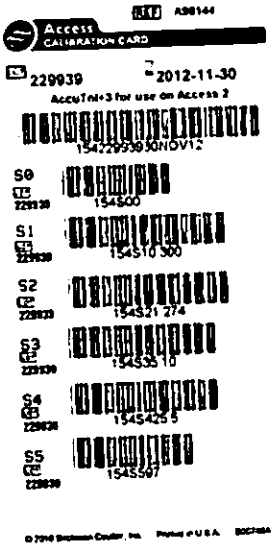

For use on Access 2 platforms only
S2
Access AccuTnI+3
1.0 mL
-20°C
~1.7 ng/mL


For use on Access 2 platforms only
S3
Access AccuTnI+3
1.0 mL
S3
-20°C
~5.0 ng/mL


For use on Access 2 platforms only
S4
Access AccuTnI+3
1.0 mL
S4
-20°C
~25 ng/mL


For use on Access 2 platforms only
S5
Access AccuTnI+3
1.0 mL
S5
-20°C
~100 ng/mL


Access
CALIBRATION CARD
229939
2012-11-30
AccuTnI+3 for use on Access 2
S0
154500
S1
154510 300
S2
154521 274
S3
154535 10
S4
154542 5
S5
154597

136

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Thursday, June 13, 2013 5:38 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx
Attachments: AccuTnI+3 Access 2 IFU B16315A.pdf

Importance: High

Hi Paula,

Please see the attached Instructions for Use. Can you let me know if the last few requests need to be sent to the Document Mail Center?

Have a great evening.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, June 13, 2013 11:44 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Thanks,
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Thursday, June 13, 2013 12:38 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

You will find the Indication for Use Form, 510(k) Summary and the response to the additional questions (e-mailed 6/12/13) attached. We will send the revised IFU this afternoon.

Please let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, June 13, 2013 11:31 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

127

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Dear Kerrie,
If you already have the intended use statement and 510(k) Summary ready, I would be happy to get those in advance of the other documents.
Thanks,
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Wednesday, June 12, 2013 7:23 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

We will send you the documents you requested tomorrow.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 5:46 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: AccuTnI+3 Access 2 IFU word version (2).docx
Importance: High

Dear Kerrie,
Please see my suggested edits to your IFU. Let me know if you have any questions or if you would like to discuss these suggested edits.
Thanks,
Paula

I will need the 510(k) Summary, Indications for use form, the responses to the questions that I sent you and the IFU tomorrow. I am very sorry that I cannot give you more time.

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 **FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2**

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access 2
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to

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the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (μg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (μg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

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Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

145

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Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 –86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

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In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

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PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

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Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[34] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL

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Substance	Highest Concentration Added
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

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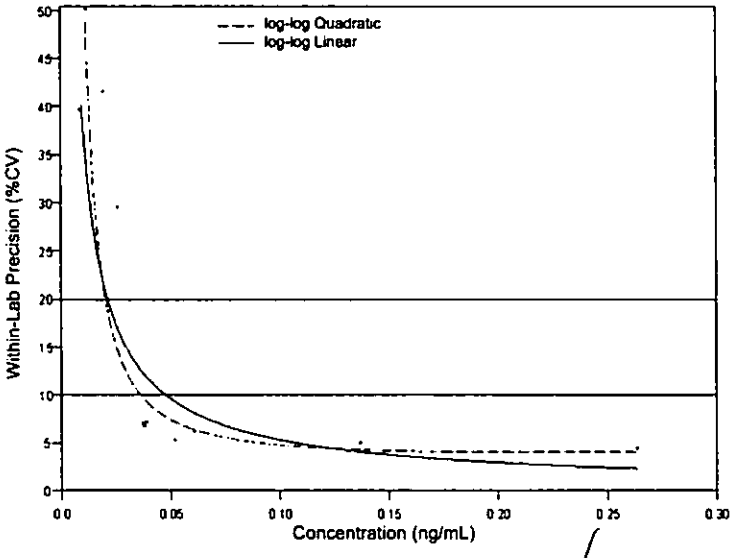
Limit of Quantitation (imprecision estimate)



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Thursday, June 13, 2013 2:13 PM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: REVISED: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity
Attachments: Response to e-mail questions June 10 A2 AI Request (6-13-13) Final.pdf

Hello Paula and Ian,

Per my phone discussion with Ian, attached is our revised proposal.

If at all possible, when the FDA makes a decision (either way), would it be possible to receive a scanned copy of the letter in addition to the routine letter sent via US Postal Service?

Thank you,
Scott

156

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Thermal

FDA: After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

BEC Response to Question 1

BEC has established an AccuTnI+3 Early Response Team (ERT), to closely monitor the performance of AccuTnI+3 assay for the Access2 instrument for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the AccuTnI+3 assay commercialization for the Access2 instrument, including product performance.

The AccuTnI+3 ERT facilitates real-time cross-functional surveillance of all customer feedback related to the AccuTnI+3 assay. ERT surveillance accelerates investigation into potential product performance issues during the early phase of AccuTnI+3's product release, allowing us to evaluate potential issues before reaching our traditional product escalation thresholds. Therefore, a single report of a potential product performance failure, regardless of the severity and magnitude of the failure, will be rapidly addressed by the ERT. The ERT will investigate all reports of potential "thermal insensitivity" as well as any other unexpected product performance failures.

If thermally insensitive samples are identified and confirmed on the Access2 instrument, BEC will use a risk management approach to determine the appropriate corrective action. For AccuTnI+3 assay, the probability of thermally insensitive samples causing falsely increased or decreased results, resulting in a potentially hazardous situation, has been determined to be Remote according to BEC's risk management process. Since we do not have any historical occurrence rates for this new failure mode, we will use discrete events for determination of the trigger threshold versus an occurrence rate. BEC believes that selecting a specific number of discrete events to trigger action is more conservative than selecting an occurrence rate given the lack of historical information and the large number of tests sold per year (> 28 million). BEC defines the occurrence of 1-4 annual discrete events for the potentially hazardous situation as a Remote occurrence.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s) (see **Table 1-1** below)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)

1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

The actual corrective action(s) depend on the frequency, magnitude, severity, and root cause. Several potential outcomes are possible, and would be driven by the risk assessment and CAPA. Examples of potential corrective actions are identified in **Table 1-1** below:

Table 1-1: Potential Corrective Actions in Event of Failure on the Access2 Instrument

Frequency	Potential Corrective Action
Low incidence (1-4 US annual discrete events)	Customer communication and/or Labeling Change • Technical Bulletin • Important Product Notification • Labeling change (updates to IFU) • Design Change
High incidence (5 ≤ n ≤ 49 US annual discrete events)	All of the above plus… Product CAPA Product Corrective Action escalation Communication to FDA
Very High incidence (≥ 50 US annual discrete events)	All of the above plus… Stop ship product Cease use notification to customers (with FDA agreement)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The AccuTnI+3 ERT process will rapidly identify and address any product performance issues experienced by customers, including thermally insensitive samples should they occur. This process is directed by and staffed with subject matter experts who have been intimately involved in the development of the thermal algorithm and the AccuTnI+3 reagents, and customer support of the current troponin assay. BEC is committed to this plan to ensure that appropriate action is taken in the event of any AccuTnI+3 performance failure on the Access2 instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 2: Field Precision Studies

(2)(b) FDA: Is the %CV calculated for this study an estimate of within-instrument variability?

BEC Response to Question 2b.

Yes, the % CV is an estimate of within-instrument variability.

Question 2: Field Precision Studies

(2)(c) FDA: For the external field effectiveness study, quality control materials were run in duplicate with 3 lots of reagents on 5 instruments at 5 external sites over 10 days. How many runs were run at each site?

BEC Response to Question 2c.

The number of days and number of runs for the external field effectiveness study are indicated in Table 2-1 below:

Table 2-1: External Field Effectiveness Test Sites

Site	Days	Runs
A	20	40
Q	10	20
U	10	20
S	10	20
E	10	18

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Question 2: Field Precision Studies

(2)(d) Is the %CV calculated for this study an estimate of within-lab variability?

BEC Response to Question 2d.

Yes, the %CV calculated for this study is an estimate of within-laboratory variability.

Question 3: Linearity

(3)(a) For the linearity studies provided in the December 14th response, how many replicates were analyzed with each reagent lot and instrument at each temperature?

BEC Response to Question 3.

For all of the linearity studies, including those provided in the December 14th response, 8 replicates of the high sample, 8 replicates of the low sample, and 4 replicates of each intermediate mixture of high and low were analyzed for each reagent lot and instrument at each temperature.

Question 4: Calibrator Stability

(4)(a) Can you clarify your shelf life claim? Is it 12 months?

BEC Response to Question 4.

The AccuTnI+3 Calibrator shelf life is 12 months.

Question 5: Analytical Specificity

(5)(a) Can you clarify the number of replicates tested for each control and for each sample spiked with potential interfering compounds in the additional interfering substance testing performed at 0.05 ng/mL troponin provided in the December 14th response? Is it also 5 replicates like the original protocol?

BEC Response to Question 5.

For this study, each control and each test sample were tested in replicates of 10.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 6: Cross Reactivity

(6)(a) Cross reactivity: Control and test samples were tested on 1 instrument using how many reagent lots and how many replicates?

BEC Response to Question 6.

Control and test samples were tested on the same instrument for each cross-reactant. For the December 14th response (repeat cross-reactivity testing of CKMB and Troponin T) two instruments and one reagent pack lot were used (see table 6-1, below). For the low (normal) cTnI sample, each control and each test sample were tested in replicates of 10. For the high (~0.5 ng/mL) cTnI sample, each control and each sample were tested in replicates of five.

Table 6-1: Test setup for December 14th response repeat testing

Testing Conducted	Instrument #	Reagent Pack Lot #
CKMB	502884	225961
Troponin T	500625	

In the original Submission, one reagent pack lot and six different instruments were used to complete the testing across the eight potential cross reactants and three temperature conditions (see table 6-2, below). Control and test samples were tested on the same instrument at each temperature condition. For the low (normal) cTnI sample, each control and each test sample were tested in replicates of 10. For the high (~0.5 ng/mL) cTnI sample, each control and each test sample were tested in replicates of 5.

Table 6-2: Test setup for original cross reactant testing

Testing Conducted	Test Temperature	Instrument #	Reagent Pack Lot #
8 cross reactants	18°C	402358	116678
		502884	
	NLC	500625	
		501022	
		507310	
	28°C	501007	
		502884	

Question 7: Clinical Matrix Comparison Study

(7)(a) Can you provide the Passing-Bablok regression analysis in singlicate for the samples between 0.02 and 5 ng/mL? Currently I only have the Passing Bablok regression analysis for the samples ranging from 0.02 to 20.

BEC Response to Question 7.

The following table contains the Passing –Bablok regression analyses in singlicate for the different sample concentration ranges.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 7-1: Passing Bablok Regression by Concentration Ranges

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 - 20	96	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00
0.02 - 5	93	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 0.99
0.02 - 0.4	75	1.00 (1.00 – 1.00)	0.00 (0.00 – 0.00)	r = 0.99

Question 8: Thermal Sensitivity Concordance Studies

(8)(a) For the studies listed in table 1-1 of the June 4, 2013 response, can you please provide the concentration range of samples tested for each study (i.e., pre-verification concordance study, thermal sensitivity—impact on low dose concordance/agreement; Repeat study, additional concordance studies-overall, thermal sensitivity-impact on cross-temperature method comparison low dose and the thermal sensitivity-impact on cross-temperature method comparison full range). I do not need the range for each comparison, just the concentration range for each study.

BEC Response to Question 8.

The concentration range of samples tested for each study is provided in **Table 8-1** below.

Table 8-1: Study Concentration Ranges

Study	Range of Results	
	Low (ng/mL)	High (ng/mL)
Pre-verification Concordance Study	0.022	0.404
Thermal Sensitivity – Impact on Low Dose Concordance/Agreement: Repeat Study	0.021	0.612
Additional Concordance Studies - Overall	0.022	0.621
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Low Dose***	0.027	0.400
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Full Range***	0.027	94.147

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 9: Clinical Sensitivity/Specificity

(9)(a) Please make sure that your estimates (and the associated 95% CI) are consistent with the data provided in response to question 3d in the December 14th response (i.e., 95% CI calculated using the Exact Method). There seems to be a mistake in the ≥ 3 to 6 hours for the 0.03 cut-off. While the submission lists the 95% CI as 90.2-97.8, the package insert lists it as 90 to 99. Please correct any discrepancies in the package insert.

BEC Response to Question 9.

The files were reviewed and you are correct, there was a transcription error in the IFU. At the ≥ 3-6 hour category for the 0.03 ng/mL cutoff, the Exact method 95% CI values are 90.2 to 97.8. The IFU has been updated from the incorrect (90-99) 95% CI to the correct (90-98) 95% CI.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Thursday, June 13, 2013 12:21 PM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

Just left you a voicemail. Will you please call my cell when you receive this note?

Thank you,
Scott

612 804-1728 Cell

From: Pilcher, Ian [mailto:Ian.Pilcher@fda.hhs.gov]
Sent: Thursday, June 13, 2013 9:08 AM
To: Cundy, Scott T; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hi Scott,

Thanks for the reply. We still have concerns about Beckman's plan. While we typically don't ask for postmarket agreements from 510(k)s, this is an unusual case. This 510(k) is the result of a warning letter and 2 major recalls, and the fix that Beckman is implementing is being validated with conflicting data. In order for FDA to make a decision that this device will be as safe and effective as predicate devices we need assurance that there are mitigation steps in place to address the potential performance issues demonstrated by the conflicting validation data. In this case the mitigation consists of increased monitoring and a plan for addressing the potential performance issue should it arise.

Beckman's updated plan states that they will stop shipment and notify customers to stop using the product if there are 100 or more discreet event occurrences of thermal insensitivity. FDA believes that the threshold of 100 discrete events is too high to provide assurance that this device is safe and effective. Every event should be investigated, but a threshold of 20 or fewer discrete events for stop shipment with FDA agreement is more appropriate to provide assurance of the safety and effectiveness of this device.

Please respond by PMA eastern time today and contact me if you have any questions.

Regards,

Ian

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

176

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

Sincerely,
Scott Cundy

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Caposino, Paula

From: De, Arkendra
Sent: Thursday, June 13, 2013 11:09 AM
To: Caposino, Paula
Subject: RE: LoQ for Beckman
Attachments: Record for K121124.doc

Hi Paula,

I have no additional analyses to include, but I would like to include the attached document for the record.
If there are any other questions, please let me know.

Thanks,
Arkendra

From: Caposino, Paula
Sent: Thursday, June 13, 2013 10:52 AM
To: De, Arkendra
Subject: LoQ for Beckman

Hi Arkendra,
Did you have any analysis that you wanted me to include in the file? Otherwise I can add a note to the file that says it appears that the LoQ estimates do not change in our analysis.
Let me know. And thanks for your help on this
P

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
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10903 New Hampshire Avenue
Building 66, Room 5648
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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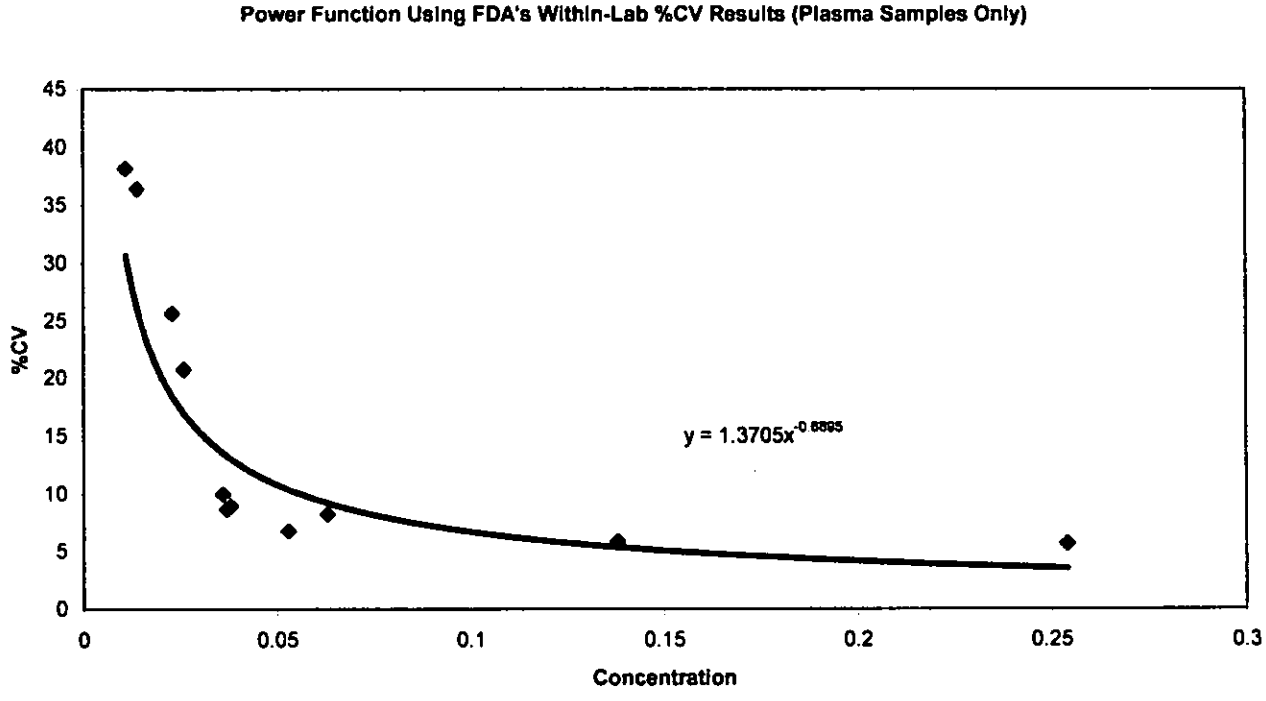
To the record:
FDA used the Excel spreasheet data from the sponsor (plasma samples only) to calculate the mean and %CV within-lab for each of the 11 samples, combining across temperature, instrument, run, and day. Below are FDA's results.

Sample ID	Mean	Within-Lab Standard Deviation	%CV
1	0.011	0.0042	38.181818
2	0.014	0.0051	36.428571
3	0.023	0.0059	25.652174
4	0.026	0.0054	20.769231
5	0.037	0.0032	8.648649
6	0.038	0.0034	8.947368
7	0.053	0.0036	6.792453
8	0.063	0.0052	8.253968
9	0.138	0.0081	5.869565
10	0.254	0.0144	5.669291
11	0.036	0.0036	10.000000

Using the above table, FDA constructed a precision profile analysis, following CLSI EP 17-A2. The below graph depicts the statistical model using the precision profile approach.



Using the equation shown in the above chart, a concentration of 0.02 yields a %CV of 20.3%, very close to the sponsor's goal of 20% CV.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 10:22 AM
To: 'Cundy, Scott T'; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: FW: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

I apologize for the typo. We would like a response by 2 PM eastern time today.

Regards,

Ian

180

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Sent: Thursday, June 13, 2013 10:08 AM
To: 'Cundy, Scott T'; Caposino, Paula
Cc: Oetter, Kerrie S
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Ian

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To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

181

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Sincerely,
Scott Cundy

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Caposino, Paula

From: Lias, Courtney H
Sent: Thursday, June 13, 2013 9:40 AM
To: Caposino, Paula; Chesler, Ruth A
Subject: FW: k121214 Decision Summary BCI Tni.doc
Attachments: k121214 Decision Summary.doc

Importance: High

Thanks. This looks good. I have a couple of easy edit suggestions.

Courtney

From: Chesler, Ruth A
Sent: Wednesday, June 12, 2013 5:37 PM
To: Lias, Courtney H
Cc: Caposino, Paula
Subject: FW: k121214 Decision Summary BCI Tni.doc
Importance: High

Courtney – can you look at the DS for Beckman TnI? It is missing a few details which Paula is waiting for answers from Beckman on but is otherwise complete.

Thanks

Ruth

From: Caposino, Paula
Sent: Wednesday, June 12, 2013 3:41 PM
To: Chesler, Ruth A
Subject: k121214 Decision Summary.doc

Here it is.
Thanks. Paula

183

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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System

G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine phosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

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2. Indication(s) for use:
   The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

   The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

   The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
   For prescription use, for *in vitro* diagnostic use, not to be used for risk stratification

4. Special instrument requirements:
   For use on the Access 2 Immunoassay System

I. Device Description:

The Access AccuTnI+3 Reagent packs contain:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300

The Access AccuTnI+3 Calibrators contain multi-point calibrators for use with the Access AccuTnI+3 Reagent. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into

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the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of troponin test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrator
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrator; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Intended Use	*in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Indications For Use	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma
Instrument	Access 2 Immunoassay System with thermal algorithm capability	ADVIA Centaur System
Specific Reagent	Mouse monoclonal anti-human	Polyclonal goat anti-

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Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Materials	cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI	cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 Reagent	Intended to calibrate the ADVIA Centaur TnI-Ultra assay

Differences		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

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L. Test Principle:

The Access AccuTnI+3 Reagent is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The sponsor evaluated precision in several studies based on CLSI EP5-A2.

The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally. A low spiked patient pool (lp), 3 commercial controls (c), and one high patient pool (hp), were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent lot.

The third study was performed externally under existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on 1 reagent lot and 1 instrument.

The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool, 3 commercial controls, and one high patient pool. These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

The following data are representative of the results from the precision studies and are presented in the labeling:

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Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of 2 per run, 2 runs per shift and 2 shifts per day. The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)
0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. This study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study, 3 instruments and 1 lot of reagent. The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1
	5	8.348	3.8

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3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate per run with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). Three sites ran a total of 20 runs, 1 site ran a total of 18 runs and 1 site ran a total of 40 runs. One instrument was used at each site. The results of the study are summarized below:

Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4
4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions (from 18 to 28 °C) using lithium heparin plasma samples spiked with native

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cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of 8 replicates of each high and each low sample were analyzed and 4 replicates of each intermediate mixture of high and low were analyzed with each reagent lot and instrument at each temperature. A total of 12 independent analyses were performed. The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The reportable range of the device is 0.02 ng/mL to 100 ng/mL.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent lots, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the different temperature conditions. The sponsor claims an LoD of 0.01 ng/mL.

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To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions.

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) < 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The reportable range of the device is 0.02 ng/mL to 100 ng/mL.

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL samples) or 10 (for the 0.05 ng/mL samples) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device.

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%
Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%
Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL,

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		13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%
Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 µg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 µg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL). Control and test samples were tested on 6 instruments and 2 reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of 10 for the low troponin samples (<0.02 ng/mL) and replicates of 5 for the high troponin samples (0.05 ng/mL). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250

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Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

f. Assay cut-off:
See section 4 "Clinical cut-off"

2. Comparison studies:

a. Method comparison:
Not applicable

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from these analyses):

Passing Bablok Regression by Concentration Ranges

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (0 to 0)	r = 1.00
0.02 to 5	93	1 (0.98 to 1.00)	0.00 (0 to 0)	r= 0.99
0.02 to 0.04	75	1 (1.00 to 1.00)	0.00 (0 to 0)	r= 0.99

Clinical concordance analysis using 123 matched samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Concordance at the 0.03 ng/mL cut-off

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

An additional matrix comparison study was performed at 3 different temperature conditions (ranging from 18°C to 28°C) on 2 instruments using 1 reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. The following are representative results (of singlicate measurements) of Passing-Bablok regression analysis and are presented in the labeling:

Range (ng/mL)	n	Slope (95% CI)	r value	Intercept (95% CI)
0.02 - 71.76	97	1.03 (1.00 - 1.05)	0.99	0.00 (-0.01 – 0.00)

3. Clinical studies:

a. *Clinical Sensitivity:*
A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline, 1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. Adjudicators were also blinded to site diagnoses. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	82.6-91.2	89.3 (1495/1675)	87.7-90.7
≥1-3 h	96.0 (119/124)	90.8-98.7	89.4 (907/1014)	87.4-91.3
≥3-6 h	94.9 (149/157)	90.2-97.8	86.7 (816/941)	84.4-88.8
≥6-9 h	90.7 (39/43)	77.9-97.4	87.0 (214/246)	82.1-90.9

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.1-60.1	97.9 (1495/1527)	97.1-98.6
≥1-3 h	52.6 (119/226)	45.9-59.3	99.5 (907/912)	98.7-99.8
≥3-6 h	54.4 (149/274)	48.3-60.4	99.0 (816/824)	98.1-99.6
≥6-9 h	54.9 (39/71)	42.7-66.8	98.2 (214/218)	95.4-99.5

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	86.2-95.3	89.1 (885/993)	87.0-91.0
≥ 8 h	94.3 (150/159)	89.5-97.4	86.8 (966/1113)	84.7-88.7

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.0-64.4	98.4 (885/899)	97.4-99.2
≥ 8 h	50.5 (150/297)	44.7-56.3	99.1 (966/975)	98.3-99.6

Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.1-95.1	84.3 (1412/1675)	82.5-86.0
≥1-3 h	98.4 (122/124)	94.3-99.8	85.5 (867/1014)	83.2-87.6
≥3-6 h	98.1 (154/157)	94.5-99.6	81.0 (762/941)	78.3-83.4
≥6-9 h	93.0 (40/43)	80.9-98.5	76.4 (188/246)	70.6-81.6

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.5-51.5	98.6 (1412/1432)	97.9-99.1
≥1-3 h	45.4 (122/269)	39.3-51.5	99.8 (867/869)	99.2-100
≥3-6 h	46.2 (154/333)	40.8-51.8	99.6 (762/765)	98.9-99.9
≥6-9 h	40.8 (40/98)	31.0-51.2	98.4 (188/191)	95.5-99.7

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	92.3-98.7	83.2 (826/993)	80.7-85.5
≥ 8 h	96.9 (154/159)	92.8-99.0	81.7 (909/1113)	79.3-83.9

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.2-54.3	99.3 (826/832)	98.4-99.7
≥ 8 h	43.0 (154/358)	37.8-48.3	99.5 (909/914)	98.7-99.8

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.4-82.1	93.9 (1572/1675)	92.6-95.0
≥1-3 h	89.5 (111/124)	82.7-94.3	93.5 (948/1014)	91.8-94.9
≥3-6 h	87.3 (137/157)	81.0-92.0	93.0 (875/941)	91.2-94.5
≥6-9 h	90.7 (39/43)	77.9-97.4	93.1 (229/246)	89.2-95.9

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	59.7-70.8	96.4 (1572/1630)	95.4-97.3
≥1-3 h	62.7 (111/177)	55.1-69.9	98.6 (948/961)	97.7-99.3
≥3-6 h	67.5 (137/203)	60.6-73.9	97.8 (875/895)	96.6-98.6
≥6-9 h	69.6 (39/56)	55.9-81.2	98.3 (229/233)	95.7-99.5

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	79.1-90.5	93.6 (929/993)	91.8-95.0
≥ 8 h	88.1 (140/159)	82.0-92.7	92.7 (1032/1113)	91.0-94.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.0-75.1	97.5 (929/953)	96.3-98.4
≥ 8 h	63.3 (140/221)	56.6-69.7	98.2 (1032/1051)	97.2-98.9

b. *Clinical specificity:*
See clinical specificity information above in 3a

c. *Other clinical supportive data (when a. and b. are not applicable):*
Not applicable

4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance

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information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included in the reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:

1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
Yes __X____ or No ____

Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X___

2. Software:
FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
Yes __X___ or No _____

3. Specimen Identification:
Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
Instructions on sample handling are provided in the reagent labeling.

5. Calibration:
An active calibration curve is required for all tests. For the Access AccuTnI+3 Reagent , calibration is required every 56 days.

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6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies to demonstrate the impact of ambient temperature differences on the test result. Three of these studies focused on troponin concentrations around the cut-offs (0.02 to 0.4 ng/mL for study 1; 0.02 to 0.6 ng/mL for studies 2 and 3). Study 4 evaluated the full reportable range (FR) of the device (0.03 to 94 ng/mL) and regression analysis of low dose (LD) samples with troponin concentrations around the cut-off (0.03 to 0.4 ng/mL) was also performed. In total, 751 lithium heparin plasma samples were tested at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperature conditions. The sponsor performed Passing-Bablok regression analyses of singlicate test results. The results of the 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98
	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00
	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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S. Other Supportive Device and Instrument Information:

Additional Linearity Study: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

Clinical matrix comparison: The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively. The sponsor concluded that this analysis demonstrated equivalent clinical performance between the matrices.

Sponsor's postmarket monitoring plan and proposed corrective action plan: This 510(k) is the result of a warning letter and 2 major recalls (please refer to the copies of the warning letter dated June 10, 2010, RES 54729, RES 58719, Beckman's reply to the warning letter dated July 14, 2010 and a copy of the urgent product correction action for the Access AccuTnI update dated June 18, 2010. All of these are enclosed). The device includes a fix validated with one set of conflicting data (see review memo documentation below). To ensure patient safety, the sponsor will implement the following plan at commercialization (please refer to a copy of the sponsors' "Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)" which is enclosed, for the sponsor's complete plan).

The sponsor has established an AccuTnI+3 Early Response Team (ERT), to monitor the performance of the device for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the device, including product performance.

If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA

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5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)
1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

T. Administrative Information:

1. *Applicant contact information:*

a. Name of applicant:	Beckman Coulter Inc.
b. Mailing address:	1000 Lake Hazeltine Drive Chaska, MN 55318
c. Phone #:	(952)368-7858
d. Fax #:	(952)368-7610
e. E-mail address (optional):	ksoetter@beckman.com
f. Contact:	Kerrie S. Oetter

2. Review documentation:
As described above in Section S, "Sponsor's postmarket monitoring plan and proposed corrective action plan", this 510(k) is the result of a warning letter and 2 major recalls and includes a fix that the sponsor is implementing (a thermal algorithm) to correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results. This algorithm is validated with one set of conflicting data. Specifically, when FDA analyzed the results from the "Thermal Sensitivity – Impact on Low Dose Concordance/Agreement study" that the sponsor provided in support of the algorithm, the estimates of the intercepts in these regressions was always 0, but, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 (95% CI of 1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 (95% CI 1.26, 1.40). In FDA's June 20, 2012 request for additional information letter, the agency expressed concern that the corrective algorithm may not resolve the thermal sensitivity from ambient temperature (please refer to the June 20, 2012 review memo). In response, the sponsor hypothesized that the anomalous results from the study were due to improper sample handling (that resulted in samples that were not thermally sensitive and thereby improperly corrected by application of the thermal algorithm), however, they did not identify a root cause for the

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unacceptable performance of the device in the temperature concordance study provided in the submission (please refer to the sponsor's December 14, 2012 response). The sponsor provided additional thermal sensitivity agreement studies in support of the algorithm (please refer to Section P of the decision summary). During the February 4, 2013 meeting with the sponsor, FDA requested an approach to make sure that the corrective algorithm is safe and effective and if it fails in the intended use setting, that the sponsor have a mechanism in place to ensure patient safety (please refer to the meeting minutes for the February 4, 2013 in-person meeting with the sponsor). On June 13, 2013, the sponsor provided their proactive approach (please refer to Section S, "Sponsor's postmarket monitoring plan and proposed corrective action plan").

3. Substantial Equivalence Discussion:

	Yes	No	
1. Same Indication Statement?		X	If **YES** = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?		X	If **YES** = Stop **NSE**
3. Same Technological Characteristics?	X		If **YES** = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If **YES** = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If **NO** = Go To 8 If **YES** = Stop **SE**
6. New Types Of Safety Or Effectiveness Questions?			If **YES** = Stop **NSE**
7. Accepted Scientific Methods Exist?			If **NO** = Stop **NSE**
8. Performance Data Available?	X		If **NO** = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: **SE**

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

a. *Explain how the new indication differs from the predicate device's indication:* The predicate device includes a claim for risk stratification, the indications for use for this device does not include this claim.

b. *Explain why there is or is not a new effect or safety or effectiveness issue:*

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

By excluding the indication for risk stratification, there is no new safety or effectiveness issue since other clinical information can be used to assess patient risk.

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:*
Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed *in vitro* diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:*
See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template sections M, P and S for more information.

U. Reviewer Name and Signature:

Paula Caposino
2013.06.14 16:52:27 -04'00'

Paula Caposino, Ph.D.
CDRH/OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** _Ian Pilcher_____

I. Product Data

Panel Code: 75 **Product Code:** MMI	**Device Name:** Access® Immunoassay Systems AccuTnI Reagent Kit when used in conjunction with UniCel DxI Access Immunoassay Systems
Model: Reagent: A78803, 33340; Calibrators: 33345	**Lot/Serial Numbers:** All lots

Marketing Status (Include 510(K) or PMA Number, Specify if Exempt From 510(K) :
k010429, k021814

Total Number of Devices In Distribution: 196,071

U.S.: 184,110 **Foreign:** 11,961

Number of Devices Subject to Recall or Review: 196,071

U.S.: 184,110 **Foreign:** 11,961

Manufacturer / Recalling Firm, Address:
Beckman Coulter, Inc.
250 S. Kraemer Blvd.
Brea, California 92821, USA

Product Description (Include Intended Use from labeling or known off-label uses):
The product being recalled is the Access® Immunoassay Systems AccuTnI Reagent Kit when used in conjunction with UniCel DxI Access Immunoassay Systems.

The manufacturer claims the following intended use: The Access® AccuTnI assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access Immunoassay Systems to aid in the diagnosis and treatment of myocardial infarction and cardiac muscle damage. Cardiac Troponin I determination also aids in the risk stratification of patients with unstable angina or non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

RES · 54729

RCL · 100161 CLASS II

34

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: 54729 **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** Ian Pilcher

II. Problem Definition and Analysis

Reason for Recall or Risk Assessment

- **Description of the Defect, Malfunction or Error in Use of the Device:**
  Beckman Coulter has confirmed customer reports that different results have been obtained from the same patient samples assayed on Access/Access 2 and UniCel DxI platforms. This is a system issue and occurs with all lots of Troponin Reagent when used in conjunction with this analyzer. Values obtained using UniCel DxI systems demonstrate a positive bias when compared to values obtained with Access® or Access® 2 systems. Troponin I test results when assayed with AccuTnI Reagent (REF 33340 and A78803) run on the UniCel DxI system have been shown to have a positive bias up to 48% when compared with results run on the Access/Access 2 systems.

- **Root Cause of the Problem (If Known):**
  The root cause is unknown and an investigation is in process.

- **Factors that May Contribute to Product Risk (i.e. Device Design, Manufacturing Problems or User Error):**
  The AccuTnI reagents have been modified several times since they received 510(k) clearance. FDA believes that some of these modifications required 510(k) clearance, but Beckman Coulter did not submit a 510(k) or notify FDA of these changes. Since FDA did not receive 510(k) submissions for the modified reagents, the performance of the device currently in distribution has not been reviewed to determine if it is substantially equivalent to a cleared device.

  Incorrect troponin test results may lead to incorrect diagnosis of acute myocardial infarction and inappropriate risk stratification of unstable angina and non-ST segment elevation acute coronary syndrome.

- **If Device Failure Occurs is it Easily Recognized by User?**
  No, this malfunction is not easily recognized unless they also test the sample on another analyzer. This malfunction does not appear to cause quality control samples to fail.

Manufacturer's CAPA Investigation (If Available):

- **Summary:**
  None submitted. CAPA in progress.

- **Date of Analysis:**
  Not applicable

- **Firm's Estimate of Number of Devices that will Develop the Defect and/or Fail :**

  - **How Many Devices from the Affected Lots Are Expected to Have or Develop the Defect?**
    All of the devices from the affected lots are expected to develop the defect when used on the DXI system.

  - **How Many Devices with the Defect are Likely to Exhibit the Failure over the Lifetime of the Device?**
    All devices are will to exhibit the failure.

  - **Of Those Devices that Fail, How Many are Likely to Cause Injury if Used?**
    The firms Health Hazard stated that the frequency of occurrence ranged from remote (defined by firm as

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<0.02 per year) to frequent (defined by firm as ≥1 but <10 per year).

- **Any Comments on How these Estimates were Reached:**
  The firm did not define how they reached these estimates.

- **Firm's Conclusion About Health Risk. (Attach a Copy of Firm's HHEs or HHAs):** The firm's documentation evaluated the following patient risks and associated hazards due to falsely elevated results on the DxI:
  - Patient is monitored longer due to false positive results. (Initial or in serial samples). Hazard: Patient is subjected to repeat testing and unnecessary specimen redraws.
  - Patient is given cardiac medications due to false positive results. (Initial or in serial samples). Hazard: Patient is exposed to unnecessary drugs. Recommended drug therapies carries inherent risks including severe bleeding.
  - False positive results. (initial or for serial samples) Hazard: Patient is subjected to repeat testing and unnecessary specimen redraws. Patient is inconvenienced by unnecessary hospital stay and medical expenses.
  - Patient is given diagnostic catheterization due to incorrect false positive results. (initial or for serial samples) Hazard: Patient is subjected to unnecessary invasive procedure.

  The firm's Hazard analyses listed multiple risk mitigation factors for these false positive results. These included the following in clinical practice: Some labs will repeat high measurements, there are clinical studies showing low risk from a low shift above the 99% URL, serial draws are used for clinical assessment, and most labs designate one system for TnI.
  They also stated that QC failures will alert customers of system bias issue, limits for total allowable error include platform bias, and clinical decision points are established as one time events, while system bias is an evaluation of trends (day to day QC).
  Additionally, they stated that bias at dose levels <0.04 ng/mL are considered negative and may be below the lower limit of detection and that the AccuTnI results should be interpreted in light of the total clinical presentation of the patient and should not serve as a stand alone diagnostic measure.
  Based on the factors above, the firm concluded that the risk caused by the defect is acceptable and define it as "as low as reasonably practicable".

- **Any FDA Comments:** FDA believes that the performance of this device has not been fully characterized. The manufacturer has made significant modifications to the reagents without notifying FDA, so FDA has not reviewed the modified reagents for safety and effectiveness or made a determination that the current device is substantially equivalent.
  FDA also believes that the falsely elevated results caused by this defect have the potential to subject patients to serious risk. Most facilities will only run this test on one analyzer, and if the analyzer is the DxI, then they will not know that the result is biased compared to the Access and they may act upon the biased result. In the worst case scenario, this may lead to unnecessary cardiac catheterization. This is an invasive procedure that is not without serious risk to the patient. It should be noted that in the risk control section of the firm's health hazard analysis, they state that QC will detect the bias, but this is only applicable to facilities running AccuTnI on the DxI and Access analyzers. Additionally, FDA believes that TnI results can be used as the primary piece of data in making patient treatment decisions, which raises the risk of unnecessary procedures being performed or medications given. It should also be noted that the bias, which has an average of 30% but has been seen up to 48%, will be seen on every TnI evaluation performed. The fact that every TnI result will be falsely elevated greatly increases the risk associated with this defect.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: 54729 **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** Ian Pilcher

Adverse Events, Complaints and Problems or Incidents that may be Related to the Device Defect:

Number of Complaints 47 **Malfunction Reports** 47

Injuries Reported **U.S.** 0 **International** 0

Deaths Reported **U.S.** 0 **International** _____

0

Sources:

Manufacturer x **Inspection** _____ **MDR's** _____

Explanation:
The manufacturer has reported 47 complaints with no adverse events reported.

Describe the Complaints and Injuries Reported to Date:
The firm reported to have received 47 customer complaints of positive bias in results with no adverse events. One of these reports documented a physician's concern that multiple results above the upper reference limit were reported.

37

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** _Ian Pilcher_____

III. Health Risks

TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

THE FOLLOWING ASSESSMENT IS BASED ON CURRENTLY AVAILABLE INFORMATION. CONCLUSIONS MAY CHANGE IF ADDITIONAL INFORMATION BECOMES AVAILABLE IN THE FUTURE.

Immediate and Long Range Health Consequences:

A. **Describe the Immediate and Long Range Health Consequences (Injuries or Illnesses) That May Result from Use of or Exposure to the Defective Device. (Include Known Off Label Uses)** Troponin is used as an essential piece of diagnostic information in the differential diagnosis of acute chest pain, shortness of breath, traumatic and post-operative cardiac injuries, in short, for the diagnosis of cardiac muscle injury. Troponin is also part of several prognostic and risk algorithms for longer term prognosis of patients with various conditions that can cause cardiac injury.

B. **Describe Any Factors That May Mitigate the Risk:** In the past, CPK-MB enzymes were measured concurrently with troponin levels. However, many clinical laboratories only measure troponin and have discontinued CPK-MB. CPK-MB used to be helpful as a separate diagnostic check on troponin assay performance. Although serial sampling for troponin detecting rising levels of troponin can be a mitigation with false elevation of troponin around the cutpoint, a single elevated troponin level together with a clinical history of chest pain (cardiac or non-cardiac in origin) may tip the balance to send a patient for catheterization in the interest of "saving myocardium" by earliest intervention. Electrocardiographic findings of acute changes can mitigate false positive troponin effects, but clinicians are taught that the electrocardiographic findings of cardiac injury may lag in time behind troponin elevation and electrocardiographic findings may be less sensitive to cardiac injuries that are less in extent than a full STEMI myocardial infarction.

C. **What Segment of the Population is Most at Risk? (e.g. Infants, Elderly, Pregnant Women, Critically Ill Patients, Immunocompromised, etc.)** Any patient who is being clinically evaluated for cardiac injury. The majority will be middle-aged to elderly adults, but some physicians may order troponin on the pediatric age group.

D. **Does the Health Consequence Have Significant Public Health Impact Beyond Users (e.g. Spread of Serious Infection to Others)?** No.

Assess the Hazards Associated with Use of the Defective Product

Check All that Might Occur:

Population at Greatest Risk	Overall Population Using Device	
x	☐	Life-threatening (death has or could occur)

38

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ ORACLE #: _____ RECALL # (s): _____

Date: _____ (Month DD, YYYY) Safety Officer: _Ian Pilcher_____

x	x	Results in permanent impairment of body function or permanent damage to a body structure.
x	x	Necessitates medical or surgical intervention.
x	x	Temporary or reversible (without medical intervention).
x	x	Limited (transient, minor impairment or complaints).
☐	☐	No adverse health consequences.

Explanation: The estimation of hazard is based on the worst case scenario that a false positive, elevated troponin level could recommend a patient for unnecessary cardiac catheterization or thrombolysis therapy. These invasive therapies carry the potential for life threatening complications. While not common, the potential for these complications is only tolerated when there is a potential benefit to the patient for these invasive therapies. There is no benefit to the invasive therapies in the case of a false positive troponin result.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ **ORACLE #:** _____ **RECALL # (s):** _____

Date: _____ (Month DD, YYYY) **Safety Officer:** _Ian Pilcher_____

IV. PROBABILITY

TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

Assess the Probability that Use of, or Exposure to, Product under Recall will Cause

A. Serious Adverse Health Consequences or Death

	Overall Population Using Device	Population at Greatest Risk
Reasonable Probability	☐	x
Remote Probability	x	☐
Not Likely	☐	☐

Explanation / Comments: This estimate of serious adverse health consequence or death is based on the scenarios described under the estimation of hazard.

B. Temporary or Medically Reversible Adverse Health Consequences

	Overall Population Using Device	Population at Greatest Risk
May Cause	x	x
Not Likely to Cause	☐	☐

Explanation / Comments: If the elevated troponin results are not near the cutpoint, the false elevation of troponin level may not change the medical decisions in patients with "true" myocardial injury that will elevate the troponin levels beyond the upper limit of normal + the amount of positive bias in this troponin assay.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Center for Devices and Radiological Health

Health Hazard Evaluation ☒ Health Risk Assessment ☐

RES #: _54729_____ ORACLE #: _____ RECALL # (s): _____

Date: _____ (Month DD, YYYY) Safety Officer: _Ian Pilcher_____

Signatures	Date	Printed Name, Title and Office
Max Robinowitz MD	March 19, 2010	Max Robinowitz, MD, OIVD/DIHD
Ian Pilcher	March 19, 2010	Ian Pilcher, CSO, OIVD/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☑ Health Risk Assessment ☐

RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

I. Product Data

Panel Code:	75	**Device Name:**	Access® Immunoassay Systems (Access, Access 2, LXi 725) UniCel® DxI 800 Access® Immunoassay Systems UniCel® DxI 600 Access® Immunoassay Systems UniCel DxC 600i, 660i, 680i, 860i, 880i SYNCHRON® Access® Clinical Systems
Product Code:	JJE		
Model:	Access: 81600 Access2 : 81600N DxC600i: A25656 LXi 725: 386200 DxI 800: 973100 DxI 600: A30260 DxC 660i: A64871 DxC 680i: A64903 DxC860i: A64935 DxC 880i: A59102	**Lot/Serial Numbers:**	All devices are affected

Marketing Status (Include 510(K) or PMA Number, Specify if Exempt From 510(K) :
k922823, k023049, k023764, k060256, k042291

Total Number of Devices In Distribution: 14,401

U.S.: 4,023 **Foreign:** 10,378

Number of Devices Subject to Recall or Review: 14,401

U.S.: 4,023 **Foreign:** 10,378

Manufacturer / Recalling Firm, Address:
Beckman Coulter, Inc.
250 S. Kraemer Blvd., MS/A2.SW.01
Brea, CA, 92821, USA

Product Description (Include Intended Use from labeling or known off-label uses):
The Access/DxI Immunoassay System is an in vitro diagnostic device used for the quantitative, semi-quantitative or qualitative determination of various analyte concentrations found in human body fluids.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Center for Devices and Radiological Health

Health Hazard Evaluation ☑ Health Risk Assessment ☐

RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

II. Problem Definition and Analysis

Reason for Recall or Risk Assessment

- **Description of the Defect, Malfunction or Error in Use of the Device:**
  The manufacturer reported that some Access immunoassays are affected by ambient temperature changes and can produce inaccurate results when a system is operated within the published range. The published range specifies that the instrument can be operated properly in an ambient temperature range of 18°C to 32°C. However, Beckman Coulter is now reporting that ambient room temperature changes within the published range above may affect assay results. The magnitude of the inaccuracy varies for each affected analyte and ranges from 1.25% to 4.25% per degree C change in ambient room temperature and the affected assays can be either falsely elevated or falsely reduced depending on the change in ambient temperature and the analyte in question.

  The %change in result per degree C for each analyte are shown below:

  Access Analytes

Analyte	%change / °C
TnI	3.5
BNP	3.5
Cortisol	1.5

  UniCel DxI Analytes

Analyte	%change / °C
Vitamin B12	2.0
AFP	2.5
Estradiol	1.5
Testosterone	2.75
Ultrasensitive hGH	1.75
Cortisol	1.5
Fast TSH	1.75
Free T4	2.0
Rubella IgG	2.75
BNP	4.25
CK-MB	1.25
TPO	2.75
Free T3	3.25
Intraoperative PTH	4.25
Toxo IgG	2.75
Inhibin A	2
SHBG	4

- **Root Cause of the Problem (If Known):**
  Temperature affects the binding kinetics of immunoassays and can cause shifts of the (relative light units) RLU signal and dose. The reason for the current specification of the operating temperature range in the instructions for use is under CAPA investigation.

- **Factors that May Contribute to Product Risk (i.e. Device Design, Manufacturing Problems or User Error):**
  The device labeling states that the analyzer can be operated properly across a temperature range of 18°C to 32°C.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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so users would not suspect that changes in temperature would affect results and would be unlikely to question these erroneous results. Also, QC samples are not regularly run during the middle of shifts, so any affect on results due temperature change within a shift would not be detected by QC.

- **If Device Failure Occurs is it Easily Recognized by User?**
  Device failure will only be recognized by the user if the change in temperature is large enough to cause QC results to fall outside the expected range and this temperature change occurs at a time when QC samples will be run. Otherwise the user is unlikely to recognize the failure.

Manufacturer's CAPA Investigation (If Available):

- **Summary:**
  PAS200200190, and CAPA 5302 contain the complaint investigations into the thermal effects on the Access AccuTnI assay. The firm's investigation makes the following claims:
  1. The maximum deviation from the true AccuTnI value would be a shift of up to 0.02 ng/mL for patient sample at the 0.04 ng/mL URL at the extremes of the current specified operating temperature range.
  2. From the stated IFU the 95% CI at concentration of the 99th percentile URL (0.04 ng/mL) is 0.03 to 0.05ng/mL. At the extremes of the current specified operating temperature range the maximum expected shift for a sample at the 99th percentile URL (0.04ng/mL) would be up to 0.02 ng/mL. This would result in a dose of 0.02ng/mL.
  3. The thermal effect of the Access AccuTnI assay does not "calibrate out." That is, recalibrating at a different temperature does not correct the bias.
  4. All but one of the commercial QC materials used in the investigation are sensitive to temperature changes, providing a good indicator of large temperature shifts. The one exception found so far is a Beckman Coulter control product, which is being discontinued.

- **Date of Analysis:**
  The CAPA is currently ongoing

- **Firm's Estimate of Number of Devices that will Develop the Defect and/or Fail :**

  - **How Many Devices from the Affected Lots Are Expected to Have or Develop the Defect?**
    All affected devices are expected to have the defect.

  - **How Many Devices with the Defect are Likely to Exhibit the Failure over the Lifetime of the Device?**
    All of the devices will exhibit the defect over the lifetime of the device.

  - **Of Those Devices that Fail, How Many are Likely to Cause Injury if Used?**
    The firm's HHE stated that there is a reasonable probability that false low troponin result could lead to a serious adverse health consequence if it were reported by a laboratory. However the firm claims that the probability of a lab reporting a false negative troponin result is low. The firm did not provide any estimation of the likelihood of injury due to erroneous results from any of the other affected analytes.

  - **Any Comments on How these Estimates were Reached:**
    The firm did not report how they reached these estimates.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☑ Health Risk Assessment ☐

RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

- **Firm's Conclusion About Health Risk. (Attach a Copy of Firm's HHEs or HHAs):** The firm only reported on the health risk of a false negative troponin report, and they concluded that the risk of this malfunction is as follows:
  - For women and others with atypical occult cardiac disease, an untreated myocardial infarction due to a false negative TnI result could lead to life threatening or permanent cardiac damage.
  - In the overall population for whom TnI is ordered, a delay in treatment of myocardial infarction due to a false negative TnI result could lead to permanent cardiac damage.

- **Any FDA Comments:** The firm's HHE did not address the risk of falsely elevated troponin results or of false results with any of the other affected analytes.

Adverse Events, Complaints and Problems or Incidents that may be Related to the Device Defect:

Number of Complaints 29 **Malfunction Reports** 0

Injuries Reported **U.S.** 0 **International** 0

Deaths Reported **U.S.** 0 **International** 0

Sources:

Manufacturer _____ **Inspection** _____ **MDR's** _____

Explanation:

The manufacturer stated that retrospective analysis of complaint records since 2/27/2003 showed a total of 29 complaints that may be due to thermal sensitivity. No injuries have been reported.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Center for Devices and Radiological Health

Health Hazard Evaluation ☑ Health Risk Assessment ☐

RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

Describe the Complaints and Injuries Reported to Date:

The manufacturer provided the following summary of injuries and complaints:

Event period from 2/27/2003 through 1/18/2011. Four complaints involved erroneous patient results. Three complaints indicated that erroneous results were reported outside of the lab.

1. The complaint investigation indicated that the lab had recently relocated the instrument to a new space with low ceiling near multiple AC vents, a deviation from the Beckman Coulter installation instructions, and that the results may have been due to cooling in the lab. The lab reported marginally high results to the physicians.
2. Patient results from another lab that varied from 27.5°C to 31°C did not misclassify the patient.
3. A complaint indicated that lab temperature conditions were above the instrument operating range at the time. The patient data were not provided.
4. A lab reported that patient results were marginally elevated, but the magnitude of error did not misclassify the patients. Information on lab temperature conditions was not provided.

The remaining customer complaints involved QC results that shifted due to change in lab temperature, possibly caused by the conditions listed below:

☐ Construction in lab
☐ Lab AC shut down
☐ Lab AC blowing directly on instrument

In these cases QC results sometimes returned within range after normal temperature conditions were restored in the lab or instruments were moved out of direct air flow. There were no cases reported where false low erroneous TnI results were large enough to misclassify a patient from significant cardiac risk to no cardiac risk in all 29 complaints.

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Center for Devices and Radiological Health

Health Hazard Evaluation ☑ Health Risk Assessment ☐

RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

III. Health Risks **TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE**
THE FOLLOWING ASSESSMENT IS BASED ON CURRENTLY AVAILABLE INFORMATION. CONCLUSIONS MAY CHANGE IF ADDITIONAL INFORMATION BECOMES AVAILABLE IN THE FUTURE.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

Immediate and Long Range Health Consequences:

A. **Describe the Immediate and Long Range Health Consequences (Injuries or Illnesses) That May Result from Use of or Exposure to the Defective Device. (Include Known Off Label Uses)**

This recall involves a wide spectrum of analytes ranging from low volume, low risk to high volume, high risk analytes. Since it is beyond the scope of this health assessment to consider all possible health consequences related to erroneous results stemming from every analyte under this recall, the highest risk analyte(s) will be considered here for purposes of risk assessment. An *ad hoc* HHE committee was convened and after thorough discussion and debate, it was determined that the highest risk analyte that comes under this recall is the Access TnI (troponin I) assay. Other analytes were considered including intra-operative parathyroid hormone (iPTH) and BNP. Erroneous iPTH levels could certainly lead to significant health consequences (unnecessary removal of additional glands, additional surgical time due to further neck exploration, missed diseased gland(s) leading to the need for additional surgery); however, it is felt that erroneous cTnI levels would result in more acute and significant health consequences. Additionally, it was concluded that while erroneous BNP results could lead to misdiagnosis of congestive heart failure and erroneous prognostic/risk interpretations, this biomarker lacks the acute and urgent clinical significant of troponin values.

Cardiac troponin I (cTnI) is one of several cardiac biomarkers that can be used to aid in the diagnosis of myocardial damage/infarction (MI) – others include cardiac troponin C, cardiac troponin T, CK-MB, and myoglobin. Typically these biomarkers are ordered in the setting of other clinical indicators of disease such as chest pain and/or EKG changes suggesting acute myocardial damage. In isolation, erroneous results could lead to missed diagnosis, misdiagnosis and/or improper treatment of a life-threatening process/event. In the event of erroneous results, i.e. falsely elevated, immediate health consequences would include treating unnecessarily with procedures (i.e. cardiac catheterization) or medications (thrombolytic, anticoagulants) that carry a significant risk profile. A more significant error such as a false negative cTnI measurement could result in a missed diagnosis of cardiac injury, i.e. cardiac ischemia/myocardial infarction. Such missed diagnoses could lead to significant health risk including irreversible cardiac injury and death.

B. **Describe Any Factors That May Mitigate the Risk:**

1. While calibration and using Beckman Coulter (BC) quality control materials will not pick up the device defect due to the fact that the products are not sensitive to ambient temperature changes, using outside commercial QC materials (non-BC products) will allow for detection of the defect as these outside products are susceptible to the ambient temperature changes. However, QC samples are not regularly run during the middle of shifts, so any affect on results due temperature change within a shift would not be detected by QC.

2. Based on the CAPA investigation (see summary p. 3) the magnitude of error of cTnI levels (falsely elevated or falsely low) within a reasonably assumed change in temperature in a laboratory would not result in misclassification of patients from significant cardiac risk to no cardiac risk or vice versa.

3. Cardiac markers are typically ordered as one of several diagnostic tools used to aid in diagnosis of myocardial damage/infarction and should not be used in isolation. If erroneous patient results are generated for cTnI other diagnostic tools (including other cardiac markers, EKG) and clinical assessment should be available to override the erroneous results. However, erroneous results for cTnI could lead to less certainty about the actual diagnosis and therefore may be a confounding factor in the overall treatment decision process. Ultimately, however, the decision to treat should be made in light of total patient assessment.

C. **What Segment of the Population is Most at Risk? (e.g. Infants, Elderly, Pregnant Women, Critically Ill Patients, Immunocompromised, etc.)** The population most at risk is those patients with atypical and/or occult cardiac disease in whom clinical assessment and routine diagnostic tools are equivocal (i.e. non-ST-segment elevation acute coronary syndrome). Often woman will present with atypical cardiac symptoms.

D. **Does the Health Consequence Have Significant Public Health Impact Beyond Users (e.g. Spread of Serious Infection to Others)?** No

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Health Hazard Evaluation ☑ Health Risk Assessment ☐

RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

Assess the Hazards Associated with Use of the Defective Product

Check All that Might Occur:

Population at Greatest Risk	Overall Population Using Device	
☒	☒	Life-threatening (death has or could occur)
☒	☒	Results in permanent impairment of body function or permanent damage to a body structure.
☒	☒	Necessitates medical or surgical intervention.
☒	☒	Temporary or reversible (without medical intervention).
☒	☒	Limited (transient, minor impairment or complaints).
☐	☐	No adverse health consequences.

Explanation:
The hazard associated with the use of the defective product(s) under this recall in both "at risk" populations, when taken in isolation, could lead to life threatening or permanent injury (using cTnI as the highest risk analyte). The probability of such hazard occurring is felt to be remote based on mitigating factors; Class II recall classification is recommended (as concluded by *ad hoc* HHE committee).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

IV. PROBABILITY

TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

Assess the Probability that Use of, or Exposure to, Product under Recall will Cause

A. Serious Adverse Health Consequences or Death

	Overall Population Using Device	Population at Greatest Risk
Reasonable Probability	☐	☐
Remote Probability	☒	☒
Not Likely	☐	☐

Explanation / Comments:
Ad hoc HHE committee was convened several times to discuss classification, in addition to consultation with "in-agency" cardiologist. After reviewing the CAPA investigation and all documentation it is felt that there is a remote probability of serious health consequences resulting from the device defect under consideration. It is the opinion of the majority of members of the *ad hoc* committee that the magnitude of error that would result with the highest risk analyte (cTnI) with reasonable change in laboratory temperature would not result in misclassification of patients from significant cardiac risk to no cardiac risk or vice versa.

B. Temporary or Medically Reversible Adverse Health Consequences

	Overall Population Using Device	Population at Greatest Risk
May Cause	☒	☒
Not Likely to Cause	☐	☐

Explanation / Comments: Temporary or medically reversible adverse health consequences may occur in both "at risk" patient populations.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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RES #: _58719_____ ORACLE #: _____ RECALL # (s): _____

Date: _August 30, 2011 Safety Officer: _Ian Pilcher

Signatures	Date	Printed Name, Title and Office
	08/30/2011	Jacqueline Wieneke, MD Medical Officer, CDRH\OIVD\DCTD
	08/30/2011	Ian Pilcher, CSO CDRH\OIVD\DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER

June 18, 2010

URGENT PRODUCT CORRECTIVE ACTION
Access AccuTnI Update

Dear Laboratory Director,

In previous correspondence, we shared information with you regarding the use of our Access AccuTnI Reagent kits. This letter provides an update to that correspondence regarding its use on the Access family of immunoassay systems, including Access, Access 2, LXi 725, and DxC 600i.

AccuTnI Lot Numbers affected:

Description	REF	Lot Numbers
Access AccuTnI Reagent	33340 and A78803	All
Access AccuTnI Calibrators	33345	All

Over time, Beckman Coulter has made several changes to the Access AccuTnI Reagent in order to optimize the performance of the product. FDA has concluded that some of these changes were significant and may have affected the performance of the device in ways that were not fully characterized. Beckman Coulter is currently performing additional clinical and analytical studies to fully characterize the performance of the modified product and is working closely with FDA to resolve this issue. The studies to be performed will include a prospective clinical study to support the submission of an updated 510(k) clearance in the first half of 2011.

In consultation with the FDA, Beckman Coulter has determined that you may continue to perform testing with the above AccuTnI reagents and calibrators used on Access systems, including Access, Access 2, LXi 725 and DxC 600i while 510(k) clearance is pending. In order to mitigate the risk of the unknown performance of these products, Beckman Coulter will be actively monitoring the performance of the above reagents and calibrators during this time. Please consider following the guidelines outlined below until an updated 510(k) clearance is received:

- According to your good laboratory practice, advise clinicians to consider a patient's signs, symptoms, history, and results of other diagnostic tests when interpreting AccuTnI assay results.
- Inform clinicians and laboratory staff that the performance of the AccuTnI assay has not yet been fully characterized by Beckman Coulter.
- Report any questions or concerns you have about the performance of the AccuTnI assay to our Technical Support Center at 1-800-854-3633 or to Troponin@beckman.com. For an immediate response, please contact our Technical Support Center.

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318-1084

Telephone: (952) 448-4848
Internet: www.beckmancoulter.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Please share this information with your laboratory staff and retain this notification as part of your laboratory quality system documentation. Complete and return the enclosed response form within 10 days so we can be assured that you have received this important notification.

We understand the inconvenience that these steps may cause your laboratory. If you have any questions regarding this notification, please contact Technical Support at 1-800-854-3633 in the United States.

Thank you for your understanding, patience, and loyalty to Beckman Coulter.

Sincerely,

Nora Zerounian

Nora Zerounian
Group Manager, Corporate Quality and Regulatory Affairs

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Final DS w/ track changes

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System

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G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine ~~p~~Phosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator ~~secondary~~
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

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2. Indication(s) for use:
The Access AccuTnI+3 ~~assay~~ Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 ~~assay~~ Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
For prescription use, for *in vitro* diagnostic use, not to be used for risk stratification

4. Special instrument requirements:
For use on the Access 2 Immunoassay System

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I. Device Description:
The Access AccuTnI+3 Reagent packs contain:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrators ~~set~~ contains multi-point calibrators for use with the Access AccuTnI+3 ~~assay~~Reagent. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into

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the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of troponin test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrators
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrators; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Intended Use	~~An~~ *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma ~~to aid in the diagnosis of myocardial infarction.~~	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Indications For Use~~use~~	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma

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61

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Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Instrument	Access 2 Immunoassay System with thermal algorithm capability	ADVIA Centaur System
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 ~~assay~~Reagent.	Intended to calibrate the ADVIA Centaur TnI-Ultra assay.

Differences		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

~~Similarities~~		
~~Item~~	~~Access 2 Immunoassay System~~	~~Predicate Device (k922823/A007)~~
~~Intended Use~~	~~For the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.~~	~~Same~~
~~Operating~~	~~Micro computer controlled, random and~~	~~Same~~

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Similarities		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Principle	continuous access	
Assay Type	Enzyme immunoassays	Same
Detection	Chemiluminescent	Same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems and computer/peripheral	Same

Differences		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Thermal Algorithm Capability	Present	Not present
Assay Protocol File (APF)	AccuTnI APF with addition of the thermal algorithm and "U" command (to improve mixing of the paramagnetic particle reagent); added result suppression when instrument internal case temperature is outside 18°C to 36°C	AccuTnI APF
Software	Version 3.3	Versions 2.4-3.2
Operating Temperature	18°C to 28°C ambient	18°C to 32°C ambient

K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

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63

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L. Test Principle:

The Access AccuTnI+3 ~~assay~~ Reagent is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The sponsor evaluated precision in several studies based on CLSI EP5-A2.

   The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally. ~~-~~A low spiked patient pool (lp), 3 commercial controls (c), and one high patient pool (hp). ~~Three commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample, and 1 pooled lithium heparin plasma sample~~ were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent ~~pack~~ lot.

   The third study was performed externally under ~~normal~~ existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on ~~one~~ 1 reagent lot and ~~one~~ 1 instrument.

   The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool ~~(sp)~~, 3 commercial controls ~~(c)~~, and one high patient pool ~~(hp)~~. These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

   The following data are representative of the results from the precision studies and are presented in the labeling:

64

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Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

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The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of 2 per run, 2 runs per shift and 2 shifts per day. ~~f X in X runs per day.~~ The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)
0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. ~~The first~~This study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study, ~~and~~ 3 instruments and ~~(how many reagent lots?).~~1 lot of reagent. The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

	5	8.348	3.8
3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate ~~(how many runs)~~ per run with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). Three sites ran a total of 20 runs, 1 site ran a total of 18 runs and 1 site ran a total of 40 runs. One instrument was used at each site. The results of ~~these studies~~the study ~~are~~ are summarized below:

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Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4
4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline

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utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions (from 18 to 28 °C) using lithium heparin plasma samples spiked with native cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of 8 replicates of each high and each low sample were analyzed and 4 replicates of each intermediate mixture of high and low ~~x replicates at each level~~ were analyzed with each reagent lot and instrument at each temperature. A ~~(for a~~ total of 12 independent analyses were performed~~)~~. The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The ~~sponsor claims that the~~ reportable range of the device is 0.02 ng/mL to ~~to the S5 calibrator (approximately~~ 100 ng/mL~~)~~.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

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d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent lots~~pucks~~, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low

67

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levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the different temperature conditions. The sponsor claims ~~that the~~an LoD o~~f is~~ 0.0~~1~~08 ng/mL.

To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions. ~~Three instruments and 2 reagent lots were used in this study.~~

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) ≤ ~~equal to~~ 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The ~~sponsor claims that the~~ reportable range of the device is 0.02 ng/mL to ~~the S5 calibrator (approximately~~ 100 ng/mL~~)~~.

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL samples) or ~~X~~ 10 (for the 0.05 ng/mL samples) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device. ~~(defined as less than 10% difference between the control sample result and the test sample result).~~

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%
Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL, 13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%
Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 µg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 µg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL ~~troponin~~). Control and test samples were tested on ~~1~~ 6 instruments and ~~using X~~2 reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of ~~X~~10 for the low troponin samples (<0.02 ng/mL) and replicates of 5 for the high troponin samples (0.05 ng/mL). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that

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the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

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Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

f. Assay cut-off:
~~Refer to~~See section 4 "Clinical cut-off".

2. Comparison studies:

a. Method comparison:
Not applicable.

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from these~~is~~ analyses~~is~~):

Passing Bablok Regression by Concentration Ranges

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Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (-0 to 0)	~~R~~ r = 1.00
0.02 to 5	93	1 (0.98 to 1.00)	0.00 (0 to 0)	r= 0.99
0.02 to 0.04	75	1 (1.00 to 1.00)	0.00 (0 to 0)	r= 0.99

Clinical concordance analysis using 123 matched ~~clinical~~ samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

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Comment [PVC11R10]: Yes

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Concordance at the 0.03 ng/mL cut-off

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

~~The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively.~~

An additional matrix comparison study was performed ~~3 times, once~~ at 3 different temperatures conditions (ranging from 18°C to 28°C) on 2 instruments using ~~one~~ 1 reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. The following are representative results (of singlicate measurements) of Passing-Bablok regression analysis and are presented in the labeling: ~~Results of Passing-Bablok regression analyses of singlicate measurements are provided below:~~

Range (ng/mL)	n	Slope (95% CI)	~~R~~r value	Intercept (95% CI)
0.02 - 71.76	97	1.03~~2~~ (1.00~~0.99~~ - 1.05~~4~~)	0.99	0.00 (-0.01 – 0.00)

3. Clinical studies:

a. *Clinical Sensitivity:*
A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline, 1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. Adjudicators were also blinded to site diagnoses. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

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Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	82.6~~3.3~~-	89.3 (1495/1675)	87.7~~8~~-90.7
≥1-3 h	96.0 (119/124)	90.8~~2.5~~-	89.4 (907/1014)	87.4~~6~~-91.3
≥3-6 h	94.9 (149/157)	90.2~~1.5~~-	86.7 (816/941)	84.4~~5~~-88.8~~9~~
≥6-9 h	90.7 (39/43)	~~82.0-~~	87.0 (214/246)	~~82.8-~~

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.12-	97.9 (1495/1527)	97.12-to
≥1-3 h	52.6 (119/226)	45.96.1-	99.5 (907/912)	98.79.0-
≥3-6 h	54.4 (149/274)	48.35-	99.0 (816/824)	98.14-99.67
≥6-9 h	54.9 (39/71)	42.73.4-	98.2 (214/218)	95.46.4-

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	86.27.3-	89.1 (885/993)	87.02-91.01
≥ 8 h	94.3 (150/159)	89.590.7-	86.8 (966/1113)	84.78-88.78

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.03-	98.4 (885/899)	97.46-99.23
≥ 8 h	50.5 (150/297)	44.78-	99.1 (966/975)	98.35-99.67

Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.18-	84.3 (1412/1675)	82.56-86.0
≥1-3 h	98.4 (122/124)	96.2-	85.5 (867/1014)	83.23-87.67
≥3-6 h	98.1 (154/157)	95.9-	81.0 (762/941)	78.5-
≥6-9 h	93.0 (40/43)	85.4-	76.4 (188/246)	71.1-

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.56-	98.6 (1412/1432)	97.98.0-
≥1-3 h	45.4 (122/269)	39.34-	99.8 (867/869)	99.25-100
≥3-6 h	46.2 (154/333)	40.89-	99.6 (762/765)	98.99.2-
≥6-9 h	40.8 (40/98)	31.01-	98.4 (188/191)	95.56.7-

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	92.3-	83.2 (826/993)	80.79-85.5
≥ 8 h	96.9 (154/159)	92.84.1-	81.7 (909/1113)	79.34-83.9

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.23-	99.3 (826/832)	98.47-99.79
≥ 8 h	43.0 (154/358)	37.89-	99.5 (909/914)	98.79.5-

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) ~~of~~ <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.9-	93.9 (1572/1675)	92.7-
≥1-3 h	89.5 (111/124)	84.1-	93.5 (948/1014)	92.0-
≥3-6 h	87.3 (137/157)	82.0-	93.0 (875/941)	91.4-
≥6-9 h	90.7 (39/43)	82.0-	93.1 (229/246)	89.9-

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	59.760.0-	96.4 (1572/1630)	95.45-97.3
≥1-3 h	62.7 (111/177)	55.16-	98.6 (948/961)	97.79-99.34
≥3-6 h	67.5 (137/203)	60.61.0-	97.8 (875/895)	96.68-98.67
≥6-9 h	69.6 (39/56)	55.97.6-	98.3 (229/233)	95.76.6-

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	80.179.1-	93.6 (929/993)	91.8-
≥ 8 h	88.1 (140/159)	82.03.0-	92.7 (1032/1113)	91.02-94.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.04-75.1	97.5 (929/953)	96.35-98.45
≥ 8 h	63.3 (140/221)	56.657.0-	98.2 (1032/1051)	97.24-

b. *Clinical specificity:*
See clinical specificity information above in 3a.

c. *Other clinical supportive data (when a. and b. are not applicable):*
Not applicable

4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance

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information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) ~~of~~ <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included in the reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:

1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
Yes __X__ or No ____

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Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X__

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2. Software:
FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
Yes __X__ or No _____

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3. Specimen Identification:
Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
Instructions on sample handling are~~is~~ provided in the reagent labeling.

5. Calibration:
An active calibration curve is required for all tests. For the Access AccuTnI+3 Reagent ~~Access AccuTnI assay~~, calibration is required every 56 days.

76

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6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

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P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies to demonstrate the impact of ambient temperature differences on the test result. Three of these (3 studies focused on low dose (LD) troponin concentrations around the cut-offs (0.02 to —0.4. ng/mL for study 1; 0.02 to 0.6 ng/mL for studies 2 and 3). Study 4 evaluated the and 1 study evaluating the full reportable range (FR) of the device (FR0.03 to 94 ng/mL) and regression analysis of low dose (LD) samples with troponin concentrations around the cut-off (0.03 to 0.4 ng/mL) was also performed. In total, of the assay) to demonstrate the impact of ambient temperature differences on the test result. Seven hundred fifty one751 (751) lithium heparin plasma samples were tested in total at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperature conditionss. The sponsor analyzed the same samples run under different temperature conditionsperformed using Passing-Bablok regression analyseis of singlicate test results. The results of the 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

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Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98
	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2 LD	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3 LD	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00

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	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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S. Other Supportive Device and Instrument Information:

Additional Linearity ~~data~~Study: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For ~~the~~ 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

Clinical matrix comparison: The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively. The sponsor concluded that this analysis demonstrated equivalent clinical performance between the matrices.

Sponsor's postmarket monitoring plan and proposed corrective action plan: This 510(k) is the result of a warning letter and 2 major recalls (please refer to the copies of the warning letter dated June 10, 2010, RES 54729, RES 58719, Beckman's reply to the warning letter dated July 14, 2010 and a copy of the urgent product correction action for the Access AccuTnI update dated June 18, 2010. All of these are enclosed). The device includes a fix validated with one set of conflicting data (see review memo documentation below). To ensure patient safety, the sponsor will implement the following plan at commercialization (please refer to a copy of the sponsors' "Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)" which is enclosed, for the sponsor's complete plan).

The sponsor has established an AccuTnI+3 Early Response Team (ERT), to monitor the performance of the device for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the device, including product performance.

If US annual discrete events on the Access2 instrument – 1 to 4 (Low incidence rate)
1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)
1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility

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3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)
1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

T. Administrative Information:

1. *Applicant contact information:*
   a. *Name of applicant:* Beckman Coulter Inc.
   b. *Mailing address:* 1000 Lake Hazeltine Drive, Chaska, MN 55318
   c. *Phone #:* (952)368-7858
   d. *Fax #:* (952)368-7610
   e. *E-mail address (optional):* ksoetter@beckman.com
   f. *Contact:* Kerrie S. Oetter

2. Review documentation:
   ~~2.~~ As described above in Section S, "Sponsor's postmarket monitoring plan and proposed corrective action plan", this 510(k) is the result of a warning letter and 2 major recalls and includes a fix that the sponsor is implementing (a thermal algorithm) to correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results. This algorithm is validated with one set of conflicting data. Specifically, when FDA analyzed the results from the "Thermal Sensitivity – Impact on Low Dose Concordance/Agreement study" that the sponsor provided in support of the algorithm, the estimates of the intercepts in these regressions was always 0, but, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 (95% CI of 1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 (95% CI 1.26, 1.40). In FDA's June 20, 2012 request for additional information letter, the agency expressed concern that the corrective algorithm may not resolve the thermal sensitivity from ambient temperature (please refer to the June 20, 2012 review memo). In response, the sponsor hypothesized that the anomalous results from

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the study were due to improper sample handling (that resulted in samples that were not thermally sensitive and thereby improperly corrected by application of the thermal algorithm), however, they did not identify a root cause for the unacceptable performance of the device in the temperature concordance study provided in the submission (please refer to the sponsor's December 14, 2012 response). The sponsor provided additional thermal sensitivity agreement studies in support of the algorithm (please refer to Section P of the decision summary). During the February 4, 2013 meeting with the sponsor, FDA requested an approach to make sure that the corrective algorithm is safe and effective and if it fails in the intended use setting, that the sponsor have a mechanism in place to ensure patient safety (please refer to the meeting minutes for the February 4, 2013 in-person meeting with the sponsor). On June 13, 2013, the sponsor provided their proactive approach (please refer to Section S, "Sponsor's postmarket monitoring plan and proposed corrective action plan").

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3. Substantial Equivalence Discussion:

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	Yes	No	
1. Same Indication Statement?	~~X~~	X	If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?		X	If YES = Stop NSE
3. Same Technological Characteristics?	X		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	X		If NO = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: SE~~CS~~

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

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a. ~~a.~~ *Explain how the new indication differs from the predicate device's indication:*

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The predicate device includes a claim for risk stratification, the indications for use for this device does not include this claim.

b. ~~b.~~ *Explain why there is or is not a new effect or safety or effectiveness issue:* By excluding the indication for risk stratification, there is no new safety or effectiveness issue since other clinical information can be used to assess patient risk.

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:* Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed *in vitro* diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:* See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template sections M, P and S ~~—performance characteristics above~~ for more information.

U. Reviewer Name and Signature:

Paula Caposino, Ph.D.
CDRH/OIR~~VD~~/DCTD

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Ruth A. Chesler-S

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k) k121214

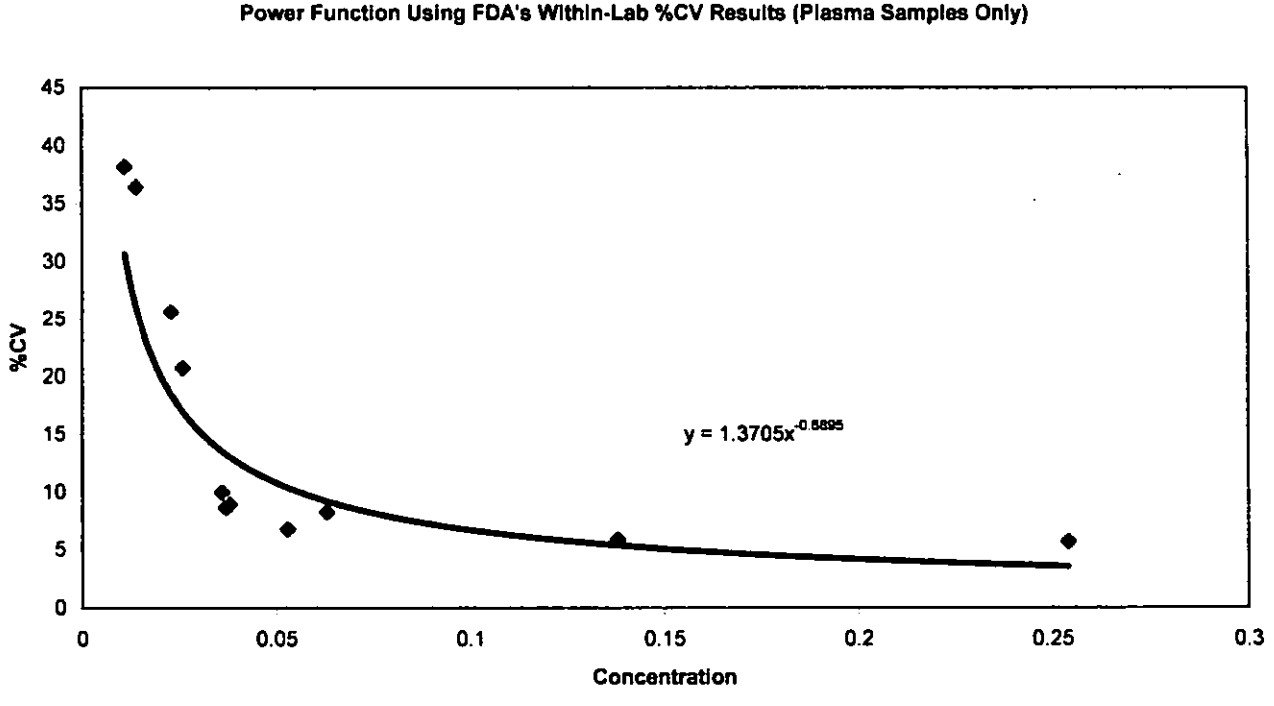
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

To: The record of k121214
From: Arkendra De, Statistician, OSB/DBS/DDB
Date: June 13, 2013
FDA used the Excel spreadsheet data [of the sponsor's LoQ studies] from the sponsor (plasma samples only) to calculate the mean and %CV within-lab for each of the 11 samples, combining across temperature, instrument, run, and day. Below are FDA's results].

Sample ID	Mean	Within-Lab Standard Deviation	%CV
1	0.011	0.0042	38.181818
2	0.014	0.0051	36.428571
3	0.023	0.0059	25.652174
4	0.026	0.0054	20.769231
5	0.037	0.0032	8.648649
6	0.038	0.0034	8.947368
7	0.053	0.0036	6.792453
8	0.063	0.0052	8.253968
9	0.138	0.0081	5.869565
10	0.254	0.0144	5.669291
11	0.036	0.0036	10.000000

Using the above table, FDA constructed a precision profile analysis, following CLSI EP 17-A2. The below graph depicts the statistical model using the precision profile approach.



Using the equation shown in the above chart, a concentration of 0.02 yields a %CV of 20.3%, very close to the sponsor's goal of 20% CV.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

RECORD OF TELECONFERENCE

Product Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System (k121214)
Sponsor: Beckman Coulter, Inc.
Meeting Date/Time: June 10, 2013 at 4 P.M.
Meeting Format: Teleconference
Meeting Recorder: Paula Caposino

FDA Attendees:
Paula Caposino, Lead Reviewer, Office Of In Vitro Diagnostics And Radiological Health (OIR), Division Of Chemistry And Toxicology Devices (DCTD)
Ian Pilcher, Reviewer, OIR/DCTD
Ruth Chesler, Cardio-Renal Branch Chief, OIR/DCTD

Beckman Coulter, Inc. Attendees:
Scott Cundy, Vice President Regulatory Affairs and Quality,
Kerrie Oetter, Senior Regulatory Affairs,
Kathy Horsfall, Senior Program Manager,
Corey Carlson, Development Manager,
Eric Hjelm, Staff Application Scientist,
Marion Navratil – Senior Manager Development and
Jeff Gibbs, Regulatory Consultant

Subject: FDA requested this teleconference with the sponsor to clarify the Agency's request regarding a proactive approach from the sponsor to ensure patient safety in case the thermal algorithm fix fails (i.e., the corrective action that they will implement in case they identify that the corrective thermal algorithm does not correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results). This request was emailed to the sponsor on June 10, 2013 (please see email dated June 10, 2013 12:59 P.M.). The agency reiterated that we are requesting a descriptive corrective action plan including a frequency threshold that will trigger the specific corrective action. FDA stated that this needs to be different from their standard complaint handling process.

Reviewer Name and Signature:

Paula Caposino
2013.06.14 13:49:24 -04'00'

Paula V. Caposino, Ph.D.
FDA/CDRH/OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

RECORD OF TELECONFERENCE

Product Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System (k121214)
Sponsor: Beckman Coulter, Inc.
Meeting Date/Time: June 13, 2013 at 1 P.M. EST
Meeting Format: Teleconference
Meeting Recorder: Paula Caposino

FDA Attendees:
Ian Pilcher, Reviewer, OIR/DCTD

Beckman Coulter, Inc. Attendees:
Scott Cundy, Vice President Regulatory Affairs and Quality,

Subject: Scott Cundy requested a call with Ian Pilcher to discuss Ian's June 13, 2013 email expressing concern with Beckman's proposed corrective plan which was emailed by the sponsor to FDA on June 13, 2013. (Please refer to the June 13, 2013 12:08 P.M. CT email from the sponsor with the proposed plan and to the June 13, 2013 10:08 AM EST email response from Ian to the sponsor). For a summary of the teleconference, please refer to Ian's internal email dated June 13, 2013 at 1:01 P.M. EST.

Reviewer Name and Signature:

Paula Caposino
2013.06.14 14:00:35 -04'00'

Paula V. Caposino, Ph.D.
FDA/CDRH/OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Friday, June 14, 2013 3:59 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Clinical Performance Summary table
Attachments: Clinical Performance Data for Exact 95.pdf

Importance: High

Dear Paula,

Attached is the Clinical Performance Data you requested. Please let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, June 14, 2013 1:31 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: Clinical Performance Summary table

OK. Let me know as soon as possible when you will have those ready.
Thanks.
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Friday, June 14, 2013 2:29 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Clinical Performance Summary table

Dear Paula,

The originator that generated the tables is not here today, so we are in the process of locating the original files. We believe we can response within two hours.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, June 14, 2013 11:58 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: FW: Clinical Performance Summary table
Importance: High

Dear Kerrie,
I realized I sent this to you to your personal email.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Please see my request below and please note that we are not asking for any changes to IFU, we just need to have the data on file.
Thanks,
'aula

Do you have an idea when I may be able to get this information?
Paula

From: Caposino, Paula
Sent: Friday, June 14, 2013 11:50 AM
To: Kerrie Oetter (koetter@live.com)
Cc: Cundy, Scott T (STCundy@beckman.com)
Subject: Clinical Performance Summary table
Importance: High

Dear Scott and Kerrie,

One last hiccup. This is the clinical performance data that I have and it seems to have Wald 95%CI and not the Exact 95% CI that are in the label.
Can you please get me all of the data with the Exact 95% CIs? Can you please make sure that the CI are not rounded up (i.e., 98.5 and not 99%).

Can you please get this to me ASAP

Thanks,

Paula

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Clinical Performance Data for Exact 95% CI

PPV and NPV for Serial Time Intervals after System Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43.2 – 54.3	99	826/832	98.4 – 99.7
	≥ 8 hours	43	154/358	37.8 – 48.3	100	909/914	98.7 – 99.8
0.03	< 8 hours	58	151/259	52.0 – 64.4	98	885/899	97.4 – 99.2
	≥ 8 hours	51	150/297	44.7 – 56.3	99	966/975	98.3 – 99.6
0.04	< 8 hours	69	141/205	62.0 – 75.1	98	929/953	96.3 – 98.4
	≥ 8 hours	63	140/221	56.6 – 69.7	98	1032/1051	97.2 – 98.9

PPV and NPV for Serial Time Intervals after Admission to the Emergency Room

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	42.5 – 51.5	99	1412/1432	97.9 – 99.1
	≥ 1 to 3	45	122/269	39.3 – 51.5*	100	867/869	99.2 – 100.0
	≥ 3 to 6	46	154/333	40.8 – 51.8	100	762/765	98.9 – 99.9
	≥ 6 to 9	41	40/98	31.0 – 51.2	98	188/191	95.5 – 99.7
0.03	Baseline	55	221/401	50.1 – 60.1	98	1495/1527	97.1 – 98.6
	≥ 1 to 3	53	119/226	45.9 – 59.3	100	907/912	98.7 – 99.8
	≥ 3 to 6	54	149/274	48.3 – 60.4	99	816/824	98.1 – 99.6
	≥ 6 to 9	55	39/71	42.7 – 66.8	98	214/218	95.4 – 99.5
0.04	Baseline	65	195/298	59.7 – 70.8	96	1572/1630	95.4 – 97.3
	≥ 1 to 3	63	111/177	55.1 – 69.9	99	948/961	97.7 – 99.3
	≥ 3 to 6	68	137/203	60.6 – 73.9	98	875/895	96.6 – 98.6
	≥ 6 to 9	70	39/56	55.9 – 81.2	98	229/233	95.7 – 99.5

*51.5– actual value is .5148 will round to 51% in IFU

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Diagnostic Sensitivity & Specificity for Serial Time after System Onset

Tnl cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92.3 – 98.7	83	826/993	80.7 – 85.5*
	≥ 8 hours	97	154/159	92.8 – 99.0	82	909/1113	79.3 – 83.9
0.03	< 8 hours	92	151/165	86.2 – 95.3	89	885/993	87.0 – 91.0
	≥ 8 hours	94	150/159	89.5 – 97.4	87	966/1113	84.7 – 88.7
0.04	< 8 hours	86	141/165	79.1 – 90.5**	94	929/993	91.8 – 95.0
	≥ 8 hours	88	140/159	82.0 – 92.7	93	1032/1113	91.0 – 94.2

*85.5 - actual value is .8546 will round to 85% in IFU

**90.5 – actual value is .9045 will round to 90% in IFU

Diagnostic Sensitivity & Specificity for Serial Time after Admission to Emergency Department

Tnl cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88.1 – 95.1	84	1412/1675	82.5 – 86.0
	≥ 1 to 3	98	122/124	94.3 – 99.8	86	867/1014	83.2 – 87.6
	≥ 3 to 6	98	154/157	94.5 – 99.6	81	762/941	78.3 – 83.4
	≥ 6 to 9	93	40/43	80.9 – 98.5	76	188/246	70.6 – 81.6
0.03	Baseline	87	221/253	82.6 – 91.2	89	1495/1675	87.7 – 90.7
	≥ 1 to 3	96	119/124	90.8 – 98.7	89	907/1014	87.4 – 91.3
	≥ 3 to 6	95	149/157	90.2 – 97.8	87	816/941	84.4 – 88.8
	≥ 6 to 9	91	39/43	77.9 – 97.4	87	214/246	82.1 – 90.9
0.04	Baseline	77	195/253	71.4 – 82.1	94	1572/1675	92.6 – 95.0
	≥ 1 to 3	90	111/124	82.7 – 94.3	94	948/1014	91.8 – 94.9
	≥ 3 to 6	87	137/157	81.0 – 92.0	93	875/941	91.2 – 94.5
	≥ 6 to 9	91	39/43	77.9 – 97.4	93	229/246	89.2 – 95.9

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Chesler, Ruth A
Sent: Friday, June 14, 2013 11:06 AM
To: Caposino, Paula
Subject: FW: k121214 Decision Summary (2).doc
Attachments: k121214 Decision Summary (2).doc

Paula – I just had some small edits –

Ruth

From: Caposino, Paula
Sent: Thursday, June 13, 2013 3:48 PM
To: Chesler, Ruth A
Cc: Lias, Courtney H
Subject: k121214 Decision Summary (2).doc

Here is the DS. I may still have to tweak some of the 95%CI confidence intervals in the clinical performance since the sponsor is making sure that they are all correct (these will be very minor tweaks). I have added all of the little details that were missing and have added a discussion of the sponsor's postmarket monitoring plan in the non-public section. Let me know if this is ok.
Thanks,
Paula

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System

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G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine pPhosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator ~~secondary~~
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

92

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2. Indication(s) for use:
The Access AccuTnI+3 ~~assay~~ Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 ~~assay~~ Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
For prescription use, for *in vitro* diagnostic use, not to be used for risk stratification

4. Special instrument requirements:
For use on the Access 2 Immunoassay System

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Comment [PVC1]: Should this be in our DS when it is not in the labeling? It is in the Pathfast DS but not in the labeling.

Comment [RAC2]: To be the same as Pathfast we should include it here

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I. Device Description:
The Access AccuTnI+3 Reagent packs contain:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrators ~~set~~ contains multi-point calibrators for use with the Access AccuTnI+3 ~~assay~~Reagent. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrators
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrators; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System	Predicate Device (k053020)
Intended Use	~~An~~ *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma. ~~to aid in the diagnosis of myocardial infarction.~~	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Indications For Use~~use~~	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma
Instrument	Access 2 Immunoassay System with thermal algorithm capability	PATHFAST Analyzer

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Comment [PVC3]: Double check with sponsor
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Comment [c4]: To be similar to pathfast, I suggest we put this is the differences table and just state the uses (one will have risk strat and one won't). There not have the risk stratification specifically called out separately.
Comment [PVC5R4]: Ruth, do you think this is acceptable or do you think I should remove Intended use altogether?
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Comment [PVC6]: Double check with sponsor
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94

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Differences		
Item	Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay System~~Access AccuTnI+3 Reagent~~	Predicate Device (k053020)
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibratorss	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 ~~assay~~Reagent~~.~~	Intended to calibrate the TnI-Ultra assay.

Differences		
Item	Access AccuTnI+3 Calibratorss	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

~~Similarities~~		
~~Item~~	~~Access 2 Immunoassay System~~	~~Predicate Device (k922823/A007)~~
~~Intended Use~~	~~For the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.~~	~~Same~~
~~Operating Principle~~	~~Micro computer controlled, random and continuous access~~	~~Same~~
~~Assay Type~~	~~Enzyme immunoassays~~	~~Same~~

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Similarities		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Detection	Chemiluminescent	Same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems and computer/peripheral	Same

Differences		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Thermal Algorithm Capability	Present	Not present
Assay Protocol File (APF)	AccuTnI APF with addition of the thermal algorithm and "U" command (to improve mixing of the paramagnetic particle reagent); added result suppression when instrument internal case temperature is outside 18°C to 36°C	AccuTnI APF
Software	Version 3.3	Versions 2.1-3.2
Operating Temperature	18°C to 28°C ambient	18°C to 32°C ambient

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K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

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L. Test Principle:

The Access AccuTnI+3 ~~assay~~ Reagent is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   The sponsor evaluated precision in several studies based on CLSI EP5-A2.

   The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally Three commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample, and 1 pooled lithium heparin plasma sample were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent pack lot.

   The third study was performed externally under ~~normal~~ existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on one reagent lot and one instrument.

   The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool (lsp), 3 commercial controls (c), and one high patient pool (hp). These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

   The following data are representative of the results from the precision studies and are presented in the labeling:

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Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

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The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of 2 per run, 2 runs per shift and 2 shifts per day. ~~f X in X runs per day.~~ The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)
0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. The first study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study ~~and~~ 3 instruments and ~~(how many reagent lots?).~~ 1 lot of reagent. The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1

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	5	8.348	3.8
3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate ~~(how many runs)~~ per run with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). Three sites ran a total of 20 runs, 1 site ran a total of 18 runs and 1 site ran a total of 40 runs. One instrument was used at each site. The results of these studies are summarized below:

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Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4
4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions

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(from 18 to 28 °C) using lithium heparin plasma samples spiked with native cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of 8 replicates of each high and each low sample were analyzed and 4 replicates of each intermediate mixture of high and low ~~x replicates at each level~~ were analyzed with each reagent lot and instrument at each temperature (for a total of 12 independent analyses). The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

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d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent packs, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the

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different temperature conditions. The sponsor claims ~~that the~~an LoD of~~is~~ 0.008 ng/mL.

To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions. Three instruments and 2 reagent lots were used in this study.

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) equal to 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL) or ~~X~~ 10 (for the 0.05 ng/mL) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device (defined as less than 10% difference between the control sample result and the test sample result).

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%
Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%

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Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL, 13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%
Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 µg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 µg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL ~~troponin~~). Control and test samples were tested on ~~1~~ 6 instruments and ~~using X~~ 2 reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of ~~X~~10 for the low troponin samples (<0.02 ng/mL) and replicates of 5 for the high troponin samples (0.05 ng/mL). For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

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Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

f. Assay cut-off:
Refer to section 4 "Clinical cut-off".

2. Comparison studies:

a. Method comparison:
Not applicable.

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from these~~is~~ analyse~~is~~):

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Passing Bablok Regression by Concentration Ranges

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (-0 to 0)	~~R~~ r = 1.00
0.02 to 5	93	1 (0.98 to 1.00)	0.00 (0 to 0)	r= 0.99
0.02 to 0.04	75	1 (1.00 to 1.00)	0.00 (0 to 0)	r= 0.99

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Clinical concordance analysis using 123 matched clinical samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

~~The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively.~~

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An additional study was performed 3 times, once at 3 different temperatures conditions (ranging from 18 to 28°C) on 2 instruments using one reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. Results of Passing-Bablok regression analyses of singlicate measurements are provided below:

Temp	Range (ng/mL)	Slope (95% CI)	R value	Intercept (95% CI)	n
18°C	0.02 - 77.96	1.03 (1.01 - 1.06)	0.99	-0.01 (-0.01 – 0.00)	97
23°C	0.02 - 71.76	1.02 (0.99 - 1.04)	0.99	0.00 (-0.01 – 0.00)	97
28°C	0.02 - 66.76	1.04 (1.01 - 1.06)	0.99	0.00 (-0.01 – 0.00)	97

3. Clinical studies:

   a. *Clinical Sensitivity:*
   A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline,

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1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	83.3-91.4	89.3 (1495/1675)	87.8-90.7
1-3 h	96.0 (119/124)	92.5-99.4	89.4 (907/1014)	87.6-91.3
3-6 h	94.9 (149/157)	91.5-98.3	86.7 (816/941)	84.5-88.9
6-9 h	90.7 (39/43)	82.0-99.4	87.0 (214/246)	82.8-91.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.2-60.0	97.9 (1495/1527)	97.2 to 98.6
1-3 h	52.6 (119/226)	46.1-59.2	99.5 (907/912)	99.0-99.9
3-6 h	54.4 (149/274)	48.5-60.3	99.0 (816/824)	98.4-99.7
6-9 h	54.9 (39/71)	43.4-66.5	98.2 (214/218)	96.4-99.9

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Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	87.3-95.8	89.1 (885/993)	87.2-91.1
≥ 8 h	94.3 (150/159)	90.7-97.9	86.8 (966/1113)	84.8-88.8

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.3-64.3	98.4 (885/899)	97.6-99.3
≥ 8 h	50.5 (150/297)	44.8-56.2	99.1 (966/975)	98.5-99.7

Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.8-95.4	84.3 (1412/1675)	82.6-86.0
1-3 h	98.4 (122/124)	96.2-100	85.5 (867/1014)	83.3-87.7
3-6 h	98.1 (154/157)	95.9-100	81.0 (762/941)	78.5-83.5
6-9 h	93.0 (40/43)	85.4-100	76.4 (188/246)	71.1-81.7

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.6-51.4	98.6 (1412/1432)	98.0-99.2
1-3 h	45.4 (122/269)	39.4-51.3	99.8 (867/869)	99.5-100
3-6 h	46.2 (154/333)	40.9-51.6	99.6 (762/765)	99.2-100
6-9 h	40.8 (40/98)	31.1-50.5	98.4 (188/191)	96.7-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	93.5-99.2	83.2 (826/993)	80.9-85.5
≥ 8 h	96.9 (154/159)	94.1-99.6	81.7 (909/1113)	79.4-83.9

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.3-54.2	99.3 (826/832)	98.7-99.9
≥ 8 h	43.0 (154/358)	37.9-48.1	99.5 (909/914)	99.5-99.9

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) of <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.9-82.3	93.9 (1572/1675)	92.7-95.0
1-3 h	89.5 (111/124)	84.1-94.9	93.5 (948/1014)	92.0-95.0
3-6 h	87.3 (137/157)	82.0-92.5	93.0 (875/941)	91.4-94.6
6-9 h	90.7 (39/43)	82.0-99.4	93.1 (229/246)	89.9-96.3

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	60.0-70.8	96.4 (1572/1630)	95.5-97.3
1-3 h	62.7 (111/177)	55.6-69.8	98.6 (948/961)	97.9-99.4
3-6 h	67.5 (137/203)	61.0-73.9	97.8 (875/895)	96.8-98.7
6-9 h	69.6 (39/56)	57.6-81.7	98.3 (229/233)	96.6-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	80.1-90.8	93.6 (929/993)	92.0-95.1
≥ 8 h	88.1 (140/159)	83.0-93.1	92.7 (1032/1113)	91.2-94.2

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Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.4-75.1	97.5 (929/953)	96.5-98.5
≥ 8 h	63.3 (140/221)	57.0-69.7	98.2 (1032/1051)	97.4-99.0

b. *Clinical specificity:*
See clinical specificity information above in 3a.

c. *Other clinical supportive data (when a. and b. are not applicable):*

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4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) of <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:
1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
Yes __X__ or No ____

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Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X__

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2. Software:
   FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
   Yes __X__ or No _____

3. Specimen Identification:
   Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
   Instruction on sample handling is provided in the reagent labeling.

5. Calibration:
   An active calibration curve is required for all tests. For the Access AccuTnI Reagent~~assay~~, calibration is required every 56 days.

6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

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P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies to demonstrate the impact of ambient temperature differences on the test result. Three of these ~~(3~~ studies focused on ~~low dose (LD)~~ troponin concentrations around the cut-offs ~~(~~0.02 to ~~—~~0.4~~.~~ ng/mL for study 1; 0.02 to 0.6 ng/mL for studies 2 and 3). Study 4 evaluated the ~~and 1 study evaluating the~~ full reportable range (FR) of the device (~~FR~~0.03 to 94 ng/mL) and regression analysis of low dose (LD) samples with troponin concentrations around the cut-off (0.03 to 0.4 ng/mL) was also performed. In total, ~~of the assay) to demonstrate the impact of ambient temperature differences on the test result. Seven hundred fifty one~~751 ~~(751)~~ lithium heparin plasma samples were tested ~~in total~~ at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperature conditions~~s~~. The sponsor analyzed the same samples run under different temperature conditions using Passing-Bablok regression analysis of singlicate test results: The results of 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

Comment [PVC15]: Check pre-verifcation is this low dose or full range, check additional concorande studies are these low dose or full range.

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Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98

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	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2 ~~LD~~	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3 ~~LD~~	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00
	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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S. Other Supportive Device and Instrument Information:

Additional Linearity ~~data~~Study: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For the 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

Clinical matrix comparison: The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively. The sponsor concluded that this analysis demonstrated equivalent clinical performance between the matrices.

Sponsor's postmarket monitoring plan: This 510(k) is the result of a warning letter and 2 recalls (please refer to the copies of the warning letter dated June 10, 2010, RES 54729 and RES 58719 included in the file of this submission) and includes a fix validated with one set of conflicting data (see review memo documentation below). To ensure patient safety, the sponsor will implement the following plan at commercialization (please refer to sponsor's response to FDA's June 10, 2013 Request for Additional Information letter for complete plan):

The sponsor has established an AccuTnI+3 Early Response Team (ERT), to monitor the performance of the device for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the device, including product performance.

If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)
1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)
1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation

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6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)
1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

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T. Administrative Information:

1. *Applicant contact information:*
   - *a. Name of applicant:* Beckman Coulter Inc.
   - *b. Mailing address:* 1000 Lake Hazeltine Drive, Chaska, MN 55318
   - *c. Phone #:* (952)368-7858
   - *d. Fax #:* (952)368-7610
   - *e. E-mail address (optional):* ksoetter@beckman.com
   - *f. Contact:* Kerrie S. Oetter

2. Review documentation:

~~2.~~ As described above in Section S, "postmarket monitoring", this 510(k) is the result of a warning letter and 2 recalls and includes a fix that the sponsor is implementing (a thermal algorithm) to correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results. This algorithm is validated with one set of conflicting data. Specifically, when FDA analyzed the results from the "Thermal Sensitivity - Impact on Low Dose Concordance/Agreement study" that the sponsor provided in support of the algorithm, the estimates of the intercepts in these regressions was always 0, but, the slope in the comparison between measurements taken at 20 and 28°C was 1.46 (95% CI of 1.36, 1.54) and for measurements taken at 18 and 26°C the slope was 1.33 (95% CI 1.26, 1.40). In FDA's June 20, 2012 request for additional information letter, the agency expressed concern that the corrective algorithm may not resolve the thermal sensitivity from ambient temperature (please refer to the June 20, 2012 review memo). In response, the sponsor hypothesized that the anomalous results from the study were due to improper sample handling (that resulted in samples that were not thermally sensitive and thereby improperly corrected by application of the thermal algorithm), however, they did not identify

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a root cause for the unacceptable performance of the device in the temperature concordance study provided in the submission (please refer to the December 14, 2012 response). The sponsor provided additional thermal sensitivity agreement studies in support of the algorithm (please refer to Section P of the decision summary). During the February 4, 2013 meeting with the sponsor, FDA requested an approach to make sure that the corrective algorithm is safe and effective and if it fails in the intended use setting, that the sponsor have a mechanism in place to ensure patient safety (please refer to the meeting minutes for the February 4, 2013 in-person meeting with the sponsor). On June 13, 2013, the sponsor provided their proactive approach (please refer to Section S, postmarket monitoring).

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3. Substantial Equivalence Discussion:

	Yes	No	
1. Same Indication Statement?	~~X~~	X	If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?		X	If YES = Stop NSE
3. Same Technological Characteristics?	X		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	X		If NO = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: CS

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

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a. ~~a.~~ *Explain how the new indication differs from the predicate device's indication:*
The predicate device includes a claim for risk stratification, the indications for use for this device does not include this claim.

b. ~~b.~~ *Explain why there is or is not a new effect or safety or effectiveness issue:*

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By excluding the indication for risk stratification, there is no new safety or effectiveness issue since other clinical information can be used to assess patient risk.

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:*
Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed *in vitro* diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:*
See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template sections M, P and S ~~—performance characteristics above~~ for more information.

U. Reviewer Name and Signature:

Paula Caposino, Ph.D.
CDRH/OIR~~VD~~/DCTD

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Friday, June 14, 2013 11:17 AM
To: Caposino, Paula; Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx
Attachments: AccuTnI+3 Access 2 IFU B16315A 2.pdf

Importance: High

Dear Paula,

BEC is brand-neutral regarding QC materials, and cannot publish recommendations regarding specific brands of commercial quality control materials without legal agreement with the manufacturers. We have added a statement, similar to that in the Limitations of the Procedure into the Quality Control section of the IFU regarding the development of the algorithm using the thermal profile of native troponin.

Please see the revised IFU which is attached.

Regards,
Kerrie Oetter

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Friday, June 14, 2013 8:35 AM
To: Cundy, Scott T
Cc: Oetter, Kerrie S
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Thanks

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Friday, June 14, 2013 8:46 AM
To: Caposino, Paula
Cc: Oetter, Kerrie S
Subject: Re: AccuTnI+3 Access 2 IFU word version (2).docx

Hello Paula,

We'll look into this and respond as quickly as possible.

Thank you,
Scott

Sent from my iPhone

On Jun 14, 2013, at 7:15 AM, "Caposino, Paula" <Paula.Caposino@fda.hhs.gov> wrote:

Dear Scott and Kerrie,

115

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Thank you very much for the information and changes to the instructions for use. One more question/suggestion:

If there are commercially available QC materials that may not be compatible with your device because they do not have the same thermal profile as native cardiac troponin I, we recommend that you somehow incorporate this information in the QC section of your labeling. Let me know.

Thanks a lot,
Paula

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty-five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance of the quality control material. The thermal profile of native human cardiac troponin I was used in development of this assay. Quality control materials containing troponin I not from this source

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(e.g. recombinant antigens) may behave differently. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects

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were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

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To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 –86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04

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ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to

125

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determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[34] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL

126

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Substance	Highest Concentration Added
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol

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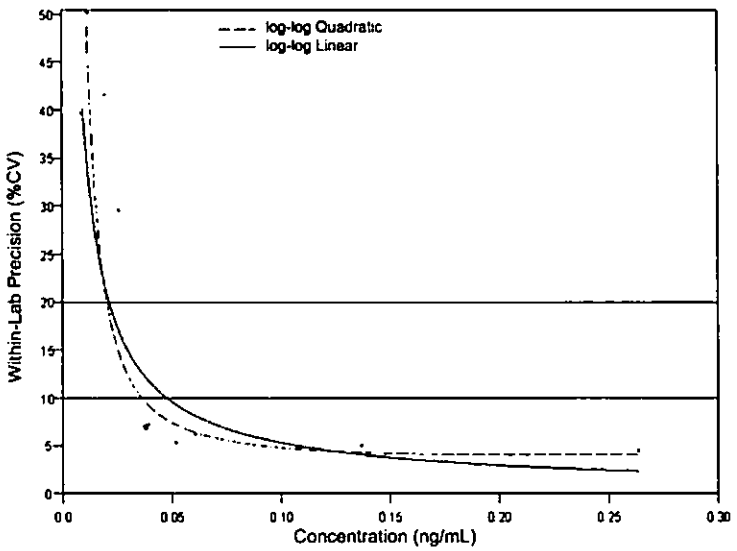
based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

Limit of Quantitation (imprecision estimate)



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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Brea, CA 92821 U.S.A.

Printed in U.S.A.
Made in U.S.A.
Issued April 2013

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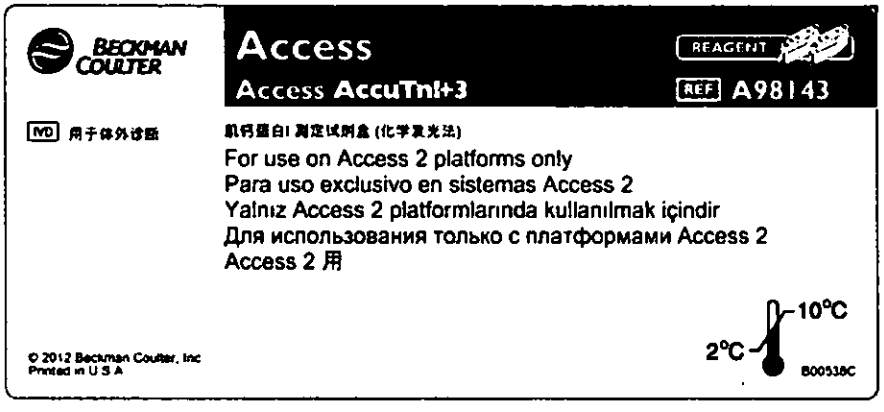
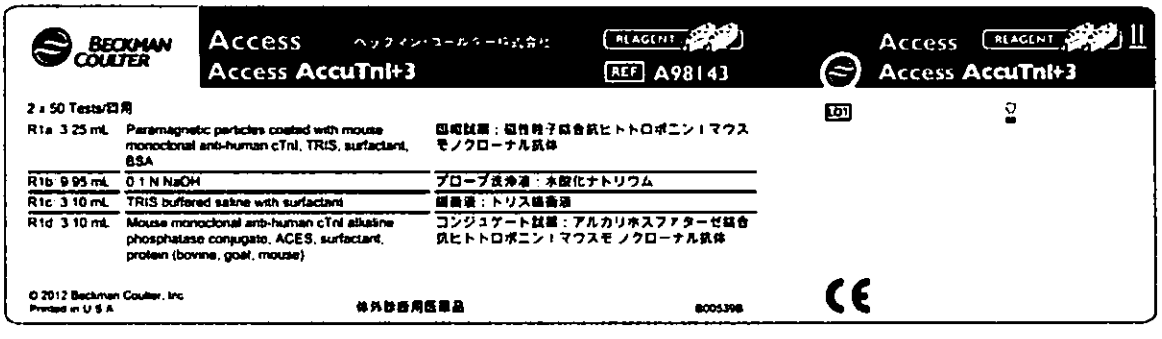
Access Reagent labels:





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Access

Access AccuTnI+3

REAGENT

REF A98143

2 reagent packs R1, for the quantitative determination of cTnI levels in human serum and plasma using the Access 2 Immunoassay Systems.

2 envases de reactivos R1, para la determinación cuantitativa de los niveles de cTnI en suero y plasma humanos utilizando los Sistemas de Inmunoensayo Access 2.

Access 2 Immunoassay Sistemlerini kullanarak insan serumu ve plazmasındaki cTnI düzeylerini nicelıksel olarak tespit etmek için 2 reaktif paketi R1.

2 комплекта реагентов R1 для количественного определения концентраций cTnI в человеческой сыворотке и плазме с использованием систем иммунного анализа Access 2.

クラスIII生化学・免疫・内分泌検査用シリーズ　トロポニンキット　/　アクセス AccuTnI 試薬パック

Xi ≥ 0.0375 – < 1.5% ProClin™ 300
R 43 S 26-37

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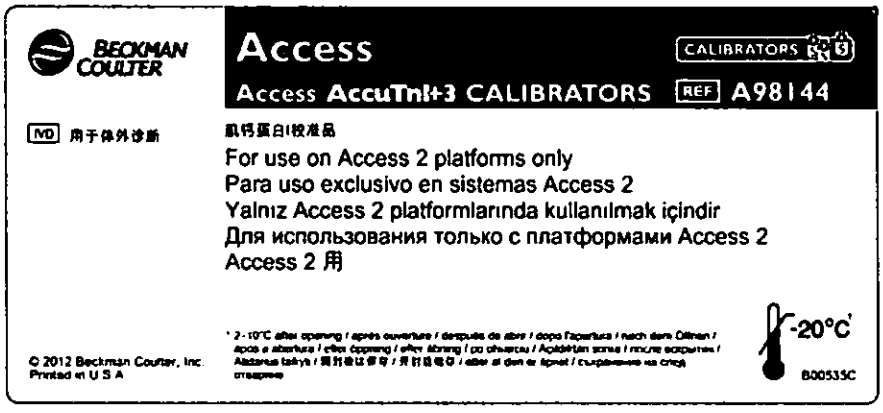
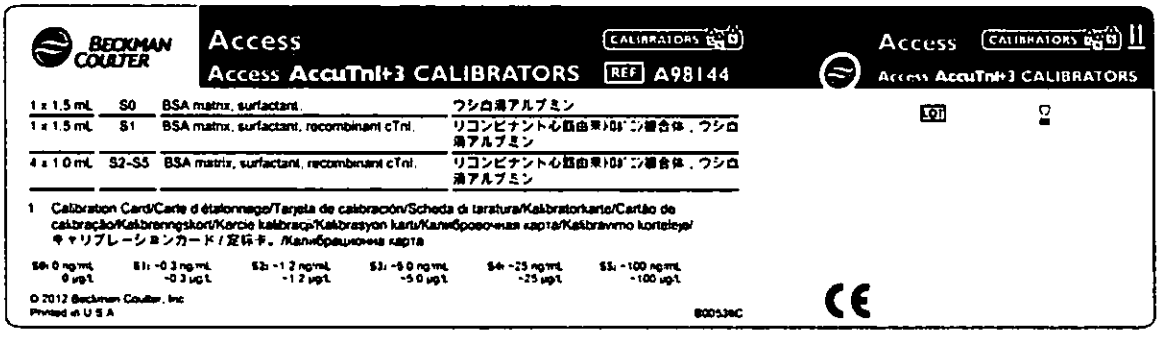
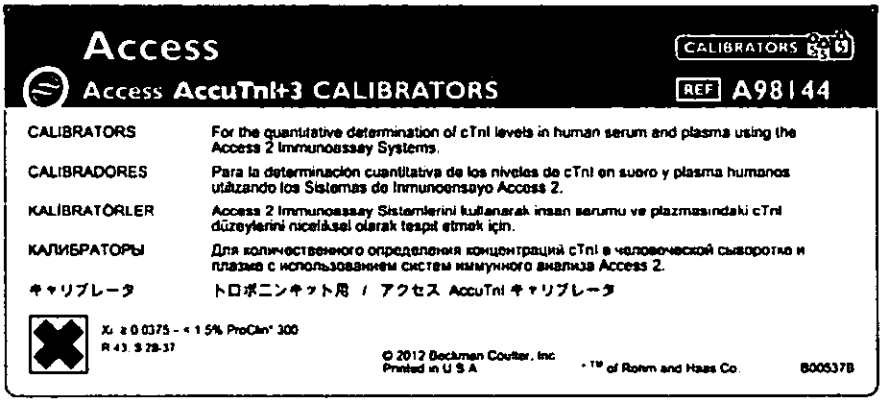
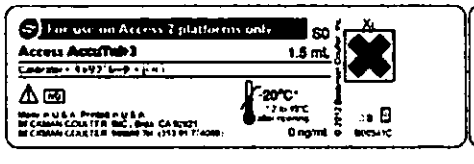
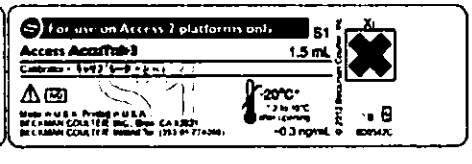
Access Calibrators:











135

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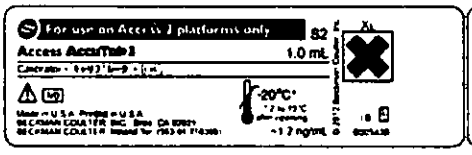
For use on Access 2 platforms only
S2
Access AccuTnI+3
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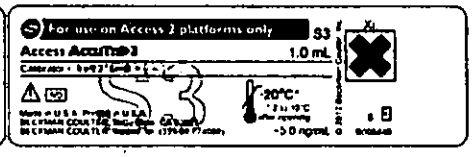
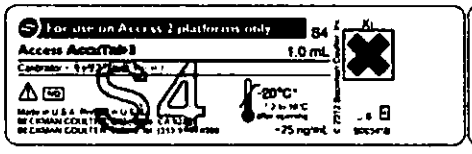
-20°C
~1.7 ng/mL


For use on Access 2 platforms only
S3
Access AccuTnI+3
1.0 mL
S3
-20°C
~5.0 ng/mL


For use on Access 2 platforms only
S4
Access AccuTnI+3
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S4
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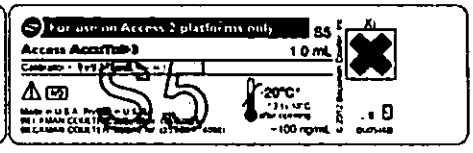
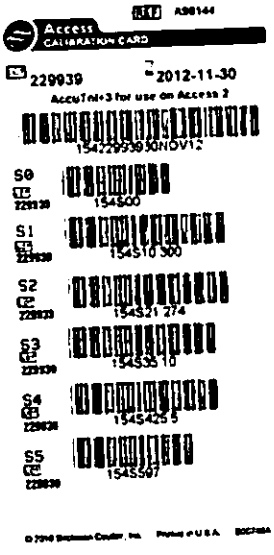
~25 ng/mL


For use on Access 2 platforms only
S5
Access AccuTnI+3
1.0 mL
S5
-20°C
~100 ng/mL


Access
CALIBRATION CARD
229939
2012-11-30
AccuTnI+3 for use on Access 2
S0
154500
S1
154510 300
S2
154521 274
S3
154535 10
S4
154542 5
S5
154597

136

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Thursday, June 13, 2013 5:38 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx
Attachments: AccuTnI+3 Access 2 IFU B16315A.pdf

Importance: High

Hi Paula,

Please see the attached Instructions for Use. Can you let me know if the last few requests need to be sent to the Document Mail Center?

Have a great evening.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, June 13, 2013 11:44 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Thanks,
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Thursday, June 13, 2013 12:38 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

You will find the Indication for Use Form, 510(k) Summary and the response to the additional questions (e-mailed 6/12/13) attached. We will send the revised IFU this afternoon.

Please let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, June 13, 2013 11:31 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

127

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Dear Kerrie,
If you already have the intended use statement and 510(k) Summary ready, I would be happy to get those in advance of the other documents.
Thanks,
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Wednesday, June 12, 2013 7:23 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

We will send you the documents you requested tomorrow.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 5:46 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: AccuTnI+3 Access 2 IFU word version (2).docx
Importance: High

Dear Kerrie,
Please see my suggested edits to your IFU. Let me know if you have any questions or if you would like to discuss these suggested edits.
Thanks,
Paula

I will need the 510(k) Summary, Indications for use form, the responses to the questions that I sent you and the IFU tomorrow. I am very sorry that I cannot give you more time.

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 **FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2**

Intended Use

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV at the 99th percentile URL make determination of a significant change more difficult, but do not cause false positive results. However, assays with CV > 20% at the 99th percentile URL should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. For use on serum and lithium heparin plasma samples. Do not dilute patient samples, as this could lead to lower than expected troponin results. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access 2
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include quality control materials that cover at least two levels of analyte. It is recommended that at least one level is targeted near the MI cutoff. Several options are commercially available that meet these criteria. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to

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the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. Ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (μg/L). Values outside of this range should be reported as < 0.02 ng/mL or > S5 calibrator (~ 100 ng/mL), respectively. Do not dilute patient samples as this could lead to lower than expected troponin results.
4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (μg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

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Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. The adjudicators were also blinded to the site diagnoses. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

145

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Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Estimates of sensitivity and specificity were determined by dividing the number of patients correctly diagnosed by the AccuTnI+3 assay (n) by the total number of patients with an adjudicated diagnosis (N). Cutoffs of 0.02 ng/mL, 0.03 ng/mL, and 0.04 ng/mL yielded 97%, 94%, and 88% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 93%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (90-97) sensitivity, and 87% (85-89) specificity. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	96	159/165	92 – 99	83	826/993	81 – 85
	≥ 8 hours	97	154/159	93 – 99	82	909/1113	79 – 84
0.03	< 8 hours	92	151/165	86 – 95	89	885/993	87 – 91
	≥ 8 hours	94	150/159	90 – 97	87	966/1113	85 – 89
0.04	< 8 hours	86	141/165	79 – 90	94	929/993	92 – 95
	≥ 8 hours	88	140/159	82 – 93	93	1032/1113	91 – 94

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)			Specificity (Non-MI patients correctly diagnosed)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	92	233/253	88 – 95	84	1412/1675	83 –86
	≥ 1 to 3	98	122/124	94 – 100	86	867/1014	83 – 88
	≥ 3 to 6	98	154/157	95 – 100	81	762/941	78 – 83
	≥ 6 to 9	93	40/43	81 – 99	76	188/246	71 – 82
0.03	Baseline	87	221/253	83 – 91	89	1495/1675	88 – 91
	≥ 1 to 3	96	119/124	91 – 99	89	907/1014	87 – 91
	≥ 3 to 6	95	149/157	90 – 98	87	816/941	84 – 89
	≥ 6 to 9	91	39/43	78 – 97	87	214/246	82 – 91
0.04	Baseline	77	195/253	71 – 82	94	1572/1675	93 – 95
	≥ 1 to 3	90	111/124	83 – 94	94	948/1014	92 – 95
	≥ 3 to 6	87	137/157	81 – 92	93	875/941	91 – 95
	≥ 6 to 9	91	39/43	78 – 97	93	229/246	89 – 96

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In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. Estimates of PPV were determined by dividing the number of patients with elevated cTnI values and adjudicated MI diagnoses (n) by the total number of patients with elevated cTnI values (N). Estimates of NPV were determined by dividing the number of patients with non-elevated cTnI values and adjudicated non-MI diagnoses (n) by the total number of patients with non-elevated cTnI values (N). NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI. The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (μg/L) at 10% CV. NPVs indicate that 96-99% of patients with cTnI values <0.04 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 63-70% of patients with cTnI values ≥ 0.04 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	< 8 hours	49	159/326	43 – 54	99	826/832	98 – 100
	≥ 8 hours	43	154/358	38 – 48	100	909/914	99 – 100
0.03	< 8 hours	58	151/259	52 – 64	98	885/899	97 – 99
	≥ 8 hours	51	150/297	45 – 56	99	966/975	98 – 100
0.04	< 8 hours	69	141/205	62 – 75	98	929/953	96 – 98
	≥ 8 hours	63	140/221	57 – 70	98	1032/1051	97 – 99

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PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)			Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)		
		%	n/N	95% CI	%	n/N	95% CI
0.02	Baseline	47	233/496	43 – 51	99	1412/1432	98 – 99
	≥ 1 to 3	45	122/269	39 – 52	100	867/869	100 – 100
	≥ 3 to 6	46	154/333	41 – 52	100	762/765	99 – 100
	≥ 6 to 9	41	40/98	31 – 51	98	188/191	95 – 100
0.03	Baseline	55	221/401	50 – 60	98	1495/1527	97 – 99
	≥ 1 to 3	53	119/226	46 – 59	100	907/912	99 – 100
	≥ 3 to 6	54	149/274	48 – 60	99	816/824	98 – 100
	≥ 6 to 9	55	39/71	43 – 67	98	214/218	95 – 100
0.04	Baseline	65	195/298	60 – 71	96	1572/1630	95 – 97
	≥ 1 to 3	63	111/177	55 – 70	99	948/961	98 – 99
	≥ 3 to 6	68	137/203	61 – 74	98	875/895	97 – 99
	≥ 6 to 9	70	39/56	56 – 81	98	229/233	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value (≥ 0.03 ng/mL) increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

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Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (approximately 0.01 ng/mL, 0.05 ng/mL, and 0.50 ng/mL). Additionally, each substance was tested at two concentrations and run on an Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[34] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). For cTnI samples ~0.50 ng/mL, the difference between the control and test samples was ≤ 10%. For cTnI samples ~0.05 ng/mL, the difference between the control and test samples was ≤ 0.006 ng/mL. For cTnI samples ~0.01 ng/mL, the control and test samples were ≤ 0.02 ng/mL. At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL

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Substance	Highest Concentration Added
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

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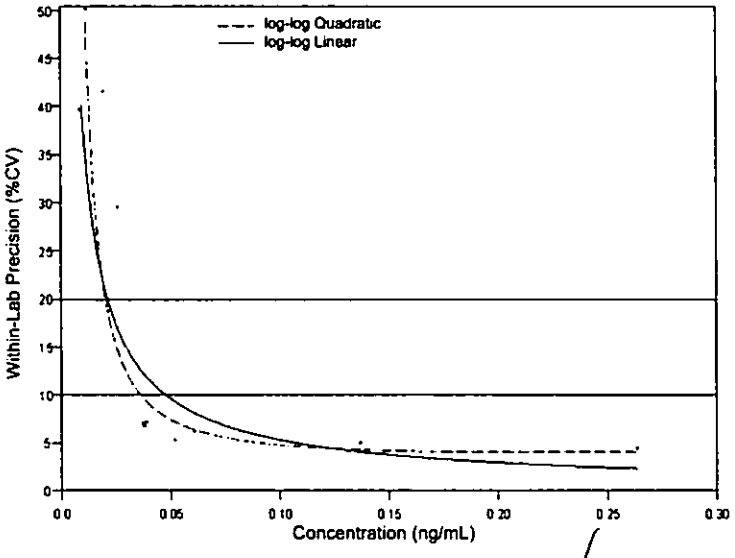
Limit of Quantitation (imprecision estimate)



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TNIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Thursday, June 13, 2013 2:13 PM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: REVISED: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity
Attachments: Response to e-mail questions June 10 A2 AI Request (6-13-13) Final.pdf

Hello Paula and Ian,

Per my phone discussion with Ian, attached is our revised proposal.

If at all possible, when the FDA makes a decision (either way), would it be possible to receive a scanned copy of the letter in addition to the routine letter sent via US Postal Service?

Thank you,
Scott

156

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Thermal

FDA: After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

BEC Response to Question 1

BEC has established an AccuTnI+3 Early Response Team (ERT), to closely monitor the performance of AccuTnI+3 assay for the Access2 instrument for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the AccuTnI+3 assay commercialization for the Access2 instrument, including product performance.

The AccuTnI+3 ERT facilitates real-time cross-functional surveillance of all customer feedback related to the AccuTnI+3 assay. ERT surveillance accelerates investigation into potential product performance issues during the early phase of AccuTnI+3's product release, allowing us to evaluate potential issues before reaching our traditional product escalation thresholds. Therefore, a single report of a potential product performance failure, regardless of the severity and magnitude of the failure, will be rapidly addressed by the ERT. The ERT will investigate all reports of potential "thermal insensitivity" as well as any other unexpected product performance failures.

If thermally insensitive samples are identified and confirmed on the Access2 instrument, BEC will use a risk management approach to determine the appropriate corrective action. For AccuTnI+3 assay, the probability of thermally insensitive samples causing falsely increased or decreased results, resulting in a potentially hazardous situation, has been determined to be Remote according to BEC's risk management process. Since we do not have any historical occurrence rates for this new failure mode, we will use discrete events for determination of the trigger threshold versus an occurrence rate. BEC believes that selecting a specific number of discrete events to trigger action is more conservative than selecting an occurrence rate given the lack of historical information and the large number of tests sold per year (> 28 million). BEC defines the occurrence of 1-4 annual discrete events for the potentially hazardous situation as a Remote occurrence.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s) (see **Table 1-1** below)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 50 (Very high incidence rate)

1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

The actual corrective action(s) depend on the frequency, magnitude, severity, and root cause. Several potential outcomes are possible, and would be driven by the risk assessment and CAPA. Examples of potential corrective actions are identified in **Table 1-1** below:

Table 1-1: Potential Corrective Actions in Event of Failure on the Access2 Instrument

Frequency	Potential Corrective Action
Low incidence (1-4 US annual discrete events)	Customer communication and/or Labeling Change • Technical Bulletin • Important Product Notification • Labeling change (updates to IFU) • Design Change
High incidence (5 ≤ n ≤ 49 US annual discrete events)	All of the above plus… Product CAPA Product Corrective Action escalation Communication to FDA
Very High incidence (≥ 50 US annual discrete events)	All of the above plus… Stop ship product Cease use notification to customers (with FDA agreement)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The AccuTnI+3 ERT process will rapidly identify and address any product performance issues experienced by customers, including thermally insensitive samples should they occur. This process is directed by and staffed with subject matter experts who have been intimately involved in the development of the thermal algorithm and the AccuTnI+3 reagents, and customer support of the current troponin assay. BEC is committed to this plan to ensure that appropriate action is taken in the event of any AccuTnI+3 performance failure on the Access2 instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(b)(4)

(b)(4)

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Thursday, June 13, 2013 12:38 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx
Attachments: 510(k) Summary AccuTnI+3 Access 2.pdf; Indications for Use Form AccuTnI Access 2.pdf; k121214 Response to June 12 A2 AI Request.pdf

Dear Paula,

You will find the Indication for Use Form, 510(k) Summary and the response to the additional questions (e-mailed 6/12/13) attached. We will send the revised IFU this afternoon.

Please let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, June 13, 2013 11:31 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Kerrie,
If you already have the intended use statement and 510(k) Summary ready, I would be happy to get those in advance of the other documents.
Thanks,
Paula

From: Oetter, Kerrie S [mailto:ksoetter@beckman.com]
Sent: Wednesday, June 12, 2013 7:23 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

We will send you the documents you requested tomorrow.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 5:46 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: AccuTnI+3 Access 2 IFU word version (2).docx
Importance: High

162

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Dear Kerrie,
Please see my suggested edits to your IFU. Let me know if you have any questions or if you would like to discuss these uggested edits.
'hanks,
Paula

I will need the 510(k) Summary, Indications for use form, the responses to the questions that I sent you and the IFU tomorrow. I am very sorry that I cannot give you more time.

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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is k121214

Submitted By:

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1142
Fax: (952) 368-7610

Contact Person:

Kerrie Oetter
1000 Lake Hazeltine Drive
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Telephone: (952) 368-7858
Fax: (952) 368-7610

Date Prepared:

June 12, 2013

Device Name:

Proprietary / Trade Name: Access AccuTnI+3 Reagent for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215
Classification Product Code: MMI

Proprietary / Trade Name: Access AccuTnI+3 Calibrator
Common Name: Calibrator
Classification Name: Calibrator
Classification Regulation: 21 CFR 862.1150
Subsequent Product Code: JIT

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160
Classification Product Code: JJE

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Predicate Devices:

The Access AccuTnI+3 Reagent and AccuTnI+3 Calibrators claim substantial equivalence to the ADVIA Centaur TnI-Ultra™ Assay and ADVIA Centaur TnI-Ultra™ Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Device Description:

The Access AccuTnI+3 reagents, AccuTnI+3 calibrators and the Access 2 Immunoassay System compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI+3 reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

The Access 2 Immunoassay System is an in vitro diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Intended Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators and the predicate device, ADVIA Centaur® TnI-Ultra™ Assay and ADVIA Centaur® TnI-Ultra™ Calibrators, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Similarities between the Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Access AccuTnI+3Calibrators
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same

Differences between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2 Immunoassay System
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized : high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.02 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.9 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.042 ng/mL	Total CV of ≤8% at concentrations >0.075 ng/mL. SD ≤0.006 at concentrations ≤0.075 ng/mL
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction. The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 System K922823/A007	New Device Access 2 Immunoassay System
Indication for Use	The Access 2 Immunoassay system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

Conclusion: The information provided above demonstrates that the new device, the Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators, have the same intended use as the predicate device. The Access 2 instrument has the same intended use as the predicate device. In addition, verification and validation testing, the clinical and analytical data, the clinical use of the product reflected in current MI diagnostic guidelines, and other scientific information provided in this submission demonstrate that the Access AccuTnI+3 Reagent, Access AccuTnI+3 Calibrators on the Access 2 Immunoassay Systems is as safe and effective as the predicate devices. Taken together, this information establishes the substantial equivalence of Beckman Coulter's products to predicates.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

_____
Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k)_____

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Responses to FDA's June 12, 2013 Request for Additional Information (e-mail AI Letter)

Question 1: Precision

FDA: Please address the following:

(1)(a) FDA: The standardized precision studies performed at 18 and 28 degrees, [where] they performed on the same instrument or on 2 separate instruments?

BEC Response to Question 1(a).

The standardized precision studies at 18 °C and 28 °C were performed on the same instrument. (Instrument #402358)

(1)(b) FDA: The precision of the device on the new multi-temperature study performed in response to FDA's original deficiency number 10 is listed as being performed over 48 runs (8 runs per temperature). Can you clarify the number of replicates per run and the number of runs per day for this study?

BEC Response to Question 1(b).

The new multi-temperature precision study included 2 replicates/run, 2 runs/shift, and 2 shifts/day. Each shift was separated by at least eight hours.

Question 2: Field Precision Studies

FDA: Please address the following:

(2)(a) FDA: For the internal field effectiveness study, how many reagent lots did you use? Do you know how many runs were run?

BEC Response to Question 2a.

A single lot of reagent was used for the internal field effectiveness study. The intent of the protocol was to replicate clinical laboratory workflow and achieve continual instrument operation during the three days of the study; therefore, the testing was not performed in discrete "runs". Instead there were approximately six hours of continuous random-access testing performed each day. Replicates of each sample (including those for non-AccuTnI+3 assays) were randomly distributed throughout each day of testing and across the incremental and dynamic temperature changes.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 2: Field Precision Studies

(2)(b) FDA: Is the %CV calculated for this study an estimate of within-instrument variability?

BEC Response to Question 2b.

Yes, the % CV is an estimate of within-instrument variability.

Question 2: Field Precision Studies

(2)(c) FDA: For the external field effectiveness study, quality control materials were run in duplicate with 3 lots of reagents on 5 instruments at 5 external sites over 10 days. How many runs were run at each site?

BEC Response to Question 2c.

The number of days and number of runs for the external field effectiveness study are indicated in Table 2-1 below:

Table 2-1: External Field Effectiveness Test Sites

Site	Days	Runs
A	20	40
Q	10	20
U	10	20
S	10	20
E	10	18

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 2: Field Precision Studies

(2)(d) Is the %CV calculated for this study an estimate of within-lab variability?

BEC Response to Question 2d.

Yes, the %CV calculated for this study is an estimate of within-laboratory variability.

Question 3: Linearity

(3)(a) For the linearity studies provided in the December 14th response, how many replicates were analyzed with each reagent lot and instrument at each temperature?

BEC Response to Question 3.

For all of the linearity studies, including those provided in the December 14th response, 8 replicates of the high sample, 8 replicates of the low sample, and 4 replicates of each intermediate mixture of high and low were analyzed for each reagent lot and instrument at each temperature.

Question 4: Calibrator Stability

(4)(a) Can you clarify your shelf life claim? Is it 12 months?

BEC Response to Question 4.

The AccuTnI+3 Calibrator shelf life is 12 months.

Question 5: Analytical Specificity

(5)(a) Can you clarify the number of replicates tested for each control and for each sample spiked with potential interfering compounds in the additional interfering substance testing performed at 0.05 ng/mL troponin provided in the December 14th response? Is it also 5 replicates like the original protocol?

BEC Response to Question 5.

For this study, each control and each test sample were tested in replicates of 10.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 6: Cross Reactivity

(6)(a) Cross reactivity: Control and test samples were tested on 1 instrument using how many reagent lots and how many replicates?

BEC Response to Question 6.

Control and test samples were tested on the same instrument for each cross-reactant. For the December 14th response (repeat cross-reactivity testing of CKMB and Troponin T) two instruments and one reagent pack lot were used (see table 6-1, below). For the low (normal) cTnI sample, each control and each test sample were tested in replicates of 10. For the high (~0.5 ng/mL) cTnI sample, each control and each sample were tested in replicates of five.

Table 6-1: Test setup for December 14th response repeat testing

Testing Conducted	Instrument #	Reagent Pack Lot #
CKMB	502884	225961
Troponin T	500625	

In the original Submission, one reagent pack lot and six different instruments were used to complete the testing across the eight potential cross reactants and three temperature conditions (see table 6-2, below). Control and test samples were tested on the same instrument at each temperature condition. For the low (normal) cTnI sample, each control and each test sample were tested in replicates of 10. For the high (~0.5 ng/mL) cTnI sample, each control and each test sample were tested in replicates of 5.

Table 6-2: Test setup for original cross reactant testing

Testing Conducted	Test Temperature	Instrument #	Reagent Pack Lot #
8 cross reactants	18°C	402358	116678
		502884	
	NLC	500625	
		501022	
		507310	
	28°C	501007	
		502884	

Question 7: Clinical Matrix Comparison Study

(7)(a) Can you provide the Passing-Bablok regression analysis in singlicate for the samples between 0.02 and 5 ng/mL? Currently I only have the Passing Bablok regression analysis for the samples ranging from 0.02 to 20.

BEC Response to Question 7.

The following table contains the Passing –Bablok regression analyses in singlicate for the different sample concentration ranges.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Table 7-1: Passing Bablok Regression by Concentration Ranges

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 - 20	96	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00
0.02 - 5	93	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 0.99
0.02 - 0.4	75	1.00 (1.00 – 1.00)	0.00 (0.00 – 0.00)	r = 0.99

Question 8: Thermal Sensitivity Concordance Studies

(8)(a) For the studies listed in table 1-1 of the June 4, 2013 response, can you please provide the concentration range of samples tested for each study (i.e., pre-verification concordance study, thermal sensitivity—impact on low dose concordance/agreement; Repeat study, additional concordance studies-overall, thermal sensitivity-impact on cross-temperature method comparison low dose and the thermal sensitivity-impact on cross-temperature method comparison full range). I do not need the range for each comparison, just the concentration range for each study.

BEC Response to Question 8.

The concentration range of samples tested for each study is provided in **Table 8-1** below.

Table 8-1: Study Concentration Ranges

Study	Range of Results	
	Low (ng/mL)	High (ng/mL)
Pre-verification Concordance Study	0.022	0.404
Thermal Sensitivity – Impact on Low Dose Concordance/Agreement: Repeat Study	0.021	0.612
Additional Concordance Studies - Overall	0.022	0.621
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Low Dose***	0.027	0.400
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Full Range***	0.027	94.147

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 9: Clinical Sensitivity/Specificity

(9)(a) Please make sure that your estimates (and the associated 95% CI) are consistent with the data provided in response to question 3d in the December 14th response (i.e., 95% CI calculated using the Exact Method). There seems to be a mistake in the ≥ 3 to 6 hours for the 0.03 cut-off. While the submission lists the 95% CI as 90.2-97.8, the package insert lists it as 90 to 99. Please correct any discrepancies in the package insert.

BEC Response to Question 9.

The files were reviewed and you are correct, there was a transcription error in the IFU. At the ≥ 3-6 hour category for the 0.03 ng/mL cutoff, the Exact method 95% CI values are 90.2 to 97.8. The IFU has been updated from the incorrect (90-99) 95% CI to the correct (90-98) 95% CI.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Thursday, June 13, 2013 12:21 PM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

Just left you a voicemail. Will you please call my cell when you receive this note?

Thank you,
Scott

612 804-1728 Cell

From: Pilcher, Ian [mailto:Ian.Pilcher@fda.hhs.gov]
Sent: Thursday, June 13, 2013 9:08 AM
To: Cundy, Scott T; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hi Scott,

Thanks for the reply. We still have concerns about Beckman's plan. While we typically don't ask for postmarket agreements from 510(k)s, this is an unusual case. This 510(k) is the result of a warning letter and 2 major recalls, and the fix that Beckman is implementing is being validated with conflicting data. In order for FDA to make a decision that this device will be as safe and effective as predicate devices we need assurance that there are mitigation steps in place to address the potential performance issues demonstrated by the conflicting validation data. In this case the mitigation consists of increased monitoring and a plan for addressing the potential performance issue should it arise.

Beckman's updated plan states that they will stop shipment and notify customers to stop using the product if there are 100 or more discreet event occurrences of thermal insensitivity. FDA believes that the threshold of 100 discrete events is too high to provide assurance that this device is safe and effective. Every event should be investigated, but a threshold of 20 or fewer discrete events for stop shipment with FDA agreement is more appropriate to provide assurance of the safety and effectiveness of this device.

Please respond by PMA eastern time today and contact me if you have any questions.

Regards,

Ian

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

176

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

Sincerely,
Scott Cundy

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Caposino, Paula

From: De, Arkendra
Sent: Thursday, June 13, 2013 11:09 AM
To: Caposino, Paula
Subject: RE: LoQ for Beckman
Attachments: Record for K121124.doc

Hi Paula,

I have no additional analyses to include, but I would like to include the attached document for the record.
If there are any other questions, please let me know.

Thanks,
Arkendra

From: Caposino, Paula
Sent: Thursday, June 13, 2013 10:52 AM
To: De, Arkendra
Subject: LoQ for Beckman

Hi Arkendra,
Did you have any analysis that you wanted me to include in the file? Otherwise I can add a note to the file that says it appears that the LoQ estimates do not change in our analysis.
Let me know. And thanks for your help on this
P

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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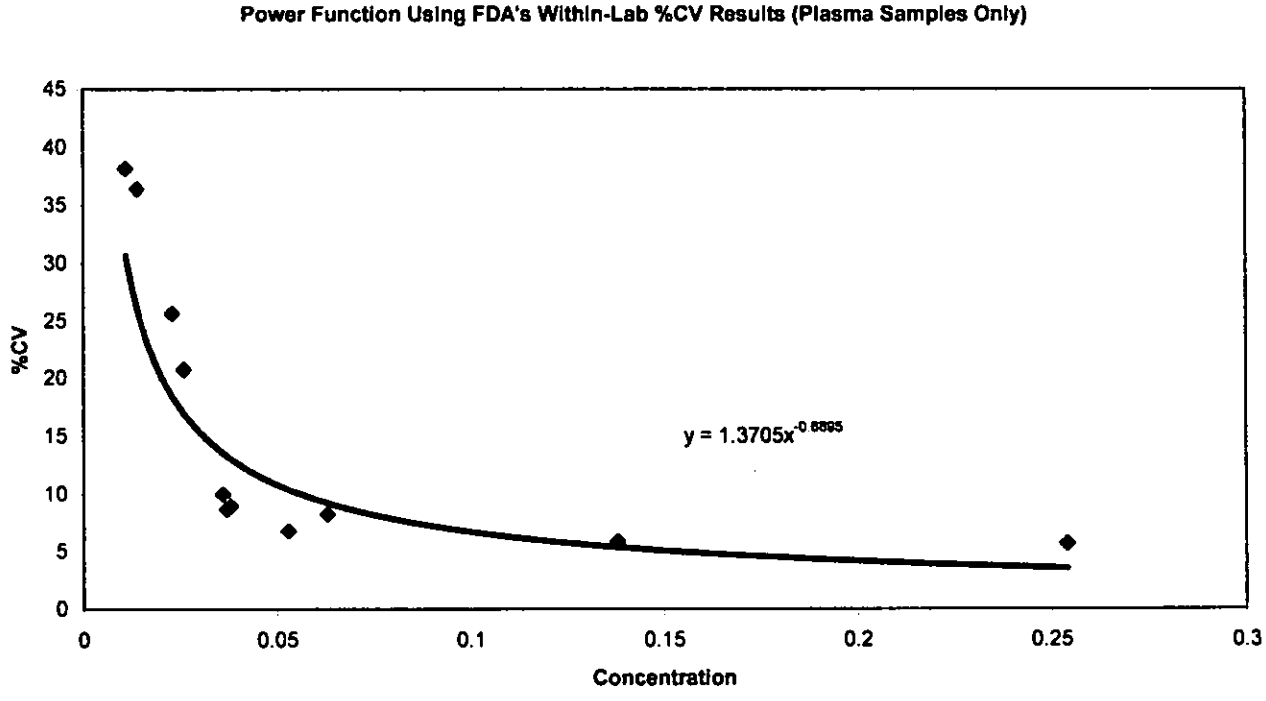
To the record:
FDA used the Excel spreasheet data from the sponsor (plasma samples only) to calculate the mean and %CV within-lab for each of the 11 samples, combining across temperature, instrument, run, and day. Below are FDA's results.

Sample ID	Mean	Within-Lab Standard Deviation	%CV
1	0.011	0.0042	38.181818
2	0.014	0.0051	36.428571
3	0.023	0.0059	25.652174
4	0.026	0.0054	20.769231
5	0.037	0.0032	8.648649
6	0.038	0.0034	8.947368
7	0.053	0.0036	6.792453
8	0.063	0.0052	8.253968
9	0.138	0.0081	5.869565
10	0.254	0.0144	5.669291
11	0.036	0.0036	10.000000

Using the above table, FDA constructed a precision profile analysis, following CLSI EP 17-A2. The below graph depicts the statistical model using the precision profile approach.



Using the equation shown in the above chart, a concentration of 0.02 yields a %CV of 20.3%, very close to the sponsor's goal of 20% CV.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 10:22 AM
To: 'Cundy, Scott T'; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: FW: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

I apologize for the typo. We would like a response by 2 PM eastern time today.

Regards,

Ian

180

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Caposino, Paula

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 10:08 AM
To: 'Cundy, Scott T'; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hi Scott,

Thanks for the reply. We still have concerns about Beckman's plan. While we typically don't ask for postmarket agreements from 510(k)s, this is an unusual case. This 510(k) is the result of a warning letter and 2 major recalls, and the fix that Beckman is implementing is being validated with conflicting data. In order for FDA to make a decision that this device will be as safe and effective as predicate devices we need assurance that there are mitigation steps in place to address the potential performance issues demonstrated by the conflicting validation data. In this case the mitigation consists of increased monitoring and a plan for addressing the potential performance issue should it arise.

Beckman's updated plan states that they will stop shipment and notify customers to stop using the product if there are 100 or more discreet event occurrences of thermal insensitivity. FDA believes that the threshold of 100 discrete events is too high to provide assurance that this device is safe and effective. Every event should be investigated, but a threshold of 20 or fewer discrete events for stop shipment with FDA agreement is more appropriate to provide assurance of the safety and effectiveness of this device.

Please respond by PMA eastern time today and contact me if you have any questions.

Regards,

Ian

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

181

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Sincerely,
Scott Cundy

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Lias, Courtney H
Sent: Thursday, June 13, 2013 9:40 AM
To: Caposino, Paula; Chesler, Ruth A
Subject: FW: k121214 Decision Summary BCI Tni.doc
Attachments: k121214 Decision Summary.doc

Importance: High

Thanks. This looks good. I have a couple of easy edit suggestions.

Courtney

From: Chesler, Ruth A
Sent: Wednesday, June 12, 2013 5:37 PM
To: Lias, Courtney H
Cc: Caposino, Paula
Subject: FW: k121214 Decision Summary BCI Tni.doc
Importance: High

Courtney – can you look at the DS for Beckman TnI? It is missing a few details which Paula is waiting for answers from Beckman on but is otherwise complete.

Thanks

Ruth

From: Caposino, Paula
Sent: Wednesday, June 12, 2013 3:41 PM
To: Chesler, Ruth A
Subject: k121214 Decision Summary.doc

Here it is.
Thanks. Paula

183

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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrator for use on the Access 2 Immunoassay System

Comment [PVC1]: Double check with sponsor

G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine Phosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator secondary
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

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2. Indication(s) for use:
The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
For prescription use, for in vitro diagnostic use, not to be used for risk stratification

Comment [PVC2]: Should this be in our DS when it is not in the labeling? It is in the Pathfast DS but not in the labeling.

Comment [RAC3]: To be the same as Pathfast we should include it here

4. Special instrument requirements:
For use on the Access 2 Immunoassay System

I. **Device Description:**
The Access AccuTnI+3 Reagent packs contain:
- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the

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system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrators
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrators; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent	Predicate Device (k053020)
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Comment [c4]: To be similar to pathfast, I suggest we put this is the differences table and just state the uses (one will have risk strat and one won't). There not have the risk stratification specifically called out separately.

Differences		
Item	Access AccuTnI+3 Reagent	Predicate Device (k053020)
Risk stratification~~Indications For Use~~ use	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate,	Polyclonal goat anti-cTnI antibody labeled with

186

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Differences		
Item	Access AccuTnI+3 Reagent	Predicate Device (k053020)
	magnetic particles coated with mouse monoclonal anti-human cTnI	acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 assay.	Intended to calibrate the TnI-Ultra assay.

Differences		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

Similarities		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Intended Use	For the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	Same
Operating Principle	Micro computer controlled, random and continuous access	Same
Assay Type	Enzyme immunoassays	Same
Detection	Chemiluminescent	Same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems and computer/peripheral	Same

Comment [c5]: Instrument? I prefer we put the instrument and assay reagents together in this description since the instrument doesn't need clearance on its own. Only the parameters here relevant to this system need to be included.

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Differences		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Thermal Algorithm Capability	Present	Not present
Assay Protocol File (APF)	AccuTnI APF with addition of the thermal algorithm and "U" command (to improve mixing of the paramagnetic particle reagent); added result suppression when instrument internal case temperature is outside 18°C to 36°C	AccuTnI APF
Software	Version 3.3	Versions 2.4-3.2
Operating Temperature	18°C to 28°C ambient	18°C to 32°C ambient

K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

L. Test Principle:

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

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M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*
The sponsor evaluated precision in several studies based on CLSI EP5-A2.

The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally Three commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample, and 1 pooled lithium heparin plasma sample were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent pack lot.

Comment [PVC6]: Or 2 instruments?

The third study was performed externally under ~~normal~~ existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on one reagent lot and one instrument.

The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool (sp), 3 commercial controls (c), and one high patient pool (hp). These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

The following data are representative of the results from the precision studies and are presented in the labeling:

Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

Comment [c7]: Sp? Or is the typo above?

The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of X in X runs per day. The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)

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0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. The first study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study and 3 instruments (how many reagent lots?). The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1
	5	8.348	3.8
3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

Comment [PVC8]: Is this true?

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate (how many runs) with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). One instrument was used at each site. The results of these studies are summarized below:

Comment [PVC9]: If you prefer Ruth, I can put in the tables with the full data instead of the range.

Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4

Comment [PVC10]: Is this true?

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4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Comment [PVC11]: Is this true?

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

Comment [PVC12]: Is this true?

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions (from 18 to 28 °C) using lithium heparin plasma samples spiked with native cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of x replicates at each level were analyzed with each reagent lot and instrument at each temperature (for a total of 12 independent analyses). The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

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Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent packs, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the different temperature conditions. The sponsor claims that the LoD is 0.008 ng/mL.

To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions. Three instruments and 2 reagent lots were used in this study.

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) equal to 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different

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temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL) or X (for the 0.05 ng/mL) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device (defined as less than 10% difference between the control sample result and the test sample result).

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%
Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%
Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL, 13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%

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Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 μg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 μg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL troponin). Control and test samples were tested on 1 instrument using X reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of X. For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

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f. Assay cut-off:
Refer to section 4 "Clinical cut-off".

2. Comparison studies:

a. Method comparison:
Not applicable.

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from this analysis):

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (0 to 0)	R = 1.00
0.02 to 5				

Comment [c13]: This row will be filled in?

Clinical concordance analysis using 123 matched clinical samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively.

Comment [c14]: I suggest we put this in the non-public section.

Comment [PVC15]: Let me know if we want to keep this in here or in the non public section

An additional study was performed 3 times, once at 3 different temperatures conditions (ranging from 18 to 28°C) on 2 instruments using one reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. Results of Passing-Bablok regression analyses of singlicate measurements are provided below:

Temp	Range (ng/mL)	Slope (95% CI)	R value	Intercept (95% CI)	n
18°C	0.02 - 77.96	1.03 (1.01 - 1.06)	0.99	-0.01 (-0.01 – 0.00)	97
23°C	0.02 - 71.76	1.02 (0.99 - 1.04)	0.99	0.00 (-0.01 – 0.00)	97
28°C	0.02 - 66.76	1.04 (1.01 - 1.06)	0.99	0.00 (-0.01 – 0.00)	97

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3. Clinical studies:

a. *Clinical Sensitivity:*

Comment [PVC16]: Sensitivity and specificity estimates a little bit different in the labeling.

A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline, 1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	83.3-91.4	89.3 (1495/1675)	87.8-90.7
1-3 h	96.0 (119/124)	92.5-99.4	89.4 (907/1014)	87.6-91.3
3-6 h	94.9 (149/157)	91.5-98.3	86.7 (816/941)	84.5-88.9
6-9 h	90.7 (39/43)	82.0-99.4	87.0 (214/246)	82.8-91.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.2-60.0	97.9 (1495/1527)	97.2 to 98.6
1-3 h	52.6 (119/226)	46.1-59.2	99.5 (907/912)	99.0-99.9
3-6 h	54.4 (149/274)	48.5-60.3	99.0 (816/824)	98.4-99.7
6-9 h	54.9 (39/71)	43.4-66.5	98.2 (214/218)	96.4-99.9

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	87.3-95.8	89.1 (885/993)	87.2-91.1
≥ 8 h	94.3 (150/159)	90.7-97.9	86.8 (966/1113)	84.8-88.8

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.3-64.3	98.4 (885/899)	97.6-99.3
≥ 8 h	50.5 (150/297)	44.8-56.2	99.1 (966/975)	98.5-99.7

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.8-95.4	84.3 (1412/1675)	82.6-86.0
1-3 h	98.4 (122/124)	96.2-100	85.5 (867/1014)	83.3-87.7
3-6 h	98.1 (154/157)	95.9-100	81.0 (762/941)	78.5-83.5
6-9 h	93.0 (40/43)	85.4-100	76.4 (188/246)	71.1-81.7

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.6-51.4	98.6 (1412/1432)	98.0-99.2
1-3 h	45.4 (122/269)	39.4-51.3	99.8 (867/869)	99.5-100
3-6 h	46.2 (154/333)	40.9-51.6	99.6 (762/765)	99.2-100
6-9 h	40.8 (40/98)	31.1-50.5	98.4 (188/191)	96.7-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	93.5-99.2	83.2 (826/993)	80.9-85.5
≥ 8 h	96.9 (154/159)	94.1-99.6	81.7 (909/1113)	79.4-83.9

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.3-54.2	99.3 (826/832)	98.7-99.9
≥ 8 h	43.0 (154/358)	37.9-48.1	99.5 (909/914)	99.5-99.9

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) of <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.9-82.3	93.9 (1572/1675)	92.7-95.0
1-3 h	89.5 (111/124)	84.1-94.9	93.5 (948/1014)	92.0-95.0
3-6 h	87.3 (137/157)	82.0-92.5	93.0 (875/941)	91.4-94.6
6-9 h	90.7 (39/43)	82.0-99.4	93.1 (229/246)	89.9-96.3

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	60.0-70.8	96.4 (1572/1630)	95.5-97.3
1-3 h	62.7 (111/177)	55.6-69.8	98.6 (948/961)	97.9-99.4
3-6 h	67.5 (137/203)	61.0-73.9	97.8 (875/895)	96.8-98.7

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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6-9 h	69.6 (39/56)	57.6-81.7	98.3 (229/233)	96.6-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	80.1-90.8	93.6 (929/993)	92.0-95.1
≥ 8 h	88.1 (140/159)	83.0-93.1	92.7 (1032/1113)	91.2-94.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.4-75.1	97.5 (929/953)	96.5-98.5
≥ 8 h	63.3 (140/221)	57.0-69.7	98.2 (1032/1051)	97.4-99.0

b. *Clinical specificity:*
See clinical specificity information above in 3a.

c. *Other clinical supportive data (when a. and b. are not applicable):*

4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) of <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:
1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Yes __X___ or No ____

Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X__

2. Software:
   FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
   Yes __X___ or No _____

3. Specimen Identification:
   Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
   Instruction on sample handling is provided in the reagent labeling.

5. Calibration:
   An active calibration curve is required for all tests. For the Access AccuTnI assay, calibration is required every 56 days.

6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies (3 studies focused on low dose (LD) troponin concentrations around the cut-offs (0.02 – 0.4. ng/mL) and 1 study evaluating the full reportable range (FR) of the assay) to demonstrate the impact of ambient temperature differences on the test result. Seven hundred fifty one (751) lithium heparin plasma samples were tested in total at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperatures. The sponsor analyzed the same samples run under different temperature conditions using Passing-Bablok analysis of singlicate test results: The results of 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

Comment [PVC17]: Check pre-verifcation is this low dose or full range, check additional concorande studies are these low dose or full range.

Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98
	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2 LD	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3 LD	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00
	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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S. Other Supportive Device and Instrument Information:

Additional Linearity data: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For the 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

T. Administrative Information:

1. *Applicant contact information:*

a. Name of applicant:	Beckman Coulter Inc.
b. Mailing address:	1000 Lake Hazeltine Drive Chaska, MN 55318
c. Phone #:	(952)368-7858
d. Fax #:	(952)368-7610
e. E-mail address (optional):	ksoetter@beckman.com
f. Contact:	Kerrie S. Oetter

2. Review documentation:

3. Substantial Equivalence Discussion:

	Yes	No	
1. Same Indication Statement?	X		If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NSE
3. Same Technological Characteristics?	X		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	X		If NO = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: CS

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for

201

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

a. *Explain how the new indication differs from the predicate device's indication:*

b. *Explain why there is or is not a new effect or safety or effectiveness issue:*

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:*
Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed in vitro diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:*
See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template section M – performance characteristics above for more information.

U. Reviewer Name and Signature:

Paula Caposino, Ph.D.
CDRH/OIVD/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Chesler, Ruth A
Sent: Thursday, June 13, 2013 8:59 AM
To: Pilcher, Ian; Caposino, Paula; Lias, Courtney H
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

I agree with Ian that each event could have multiple erroneous results, therefore I think 20- 25 would be a much better number than 100. Also I am wondering about the timeline for reporting these events to FDA if they use their standard risk evaluation and management processes – would it be the same as for MDR (which is pretty long)?

Ruth

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 8:44 AM
To: Caposino, Paula; Lias, Courtney H; Chesler, Ruth A
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

They have not proposed any additional monitoring beyond their typical complaint system and their rapid response team.

From: Caposino, Paula
Sent: Thursday, June 13, 2013 8:38 AM
To: Lias, Courtney H; Pilcher, Ian; Chesler, Ruth A
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

I worry about agreeing with the upper limit of 100 as well. I think it is good that FDA will be informed at the 5 threshold.
Would we consider having them lower the threshold to 20ish but change the corrective action to:
All of the above plus…
Stop ship product (with FDA agreement)
Cease use notification to customers (with FDA agreement)
That way we can discuss at that time if that is a reasonable corrective action.

Have they proposed monitoring? I don't believe that they have unless we consider this rapid response team as monitoring.

Thanks.
Paula

From: Lias, Courtney H
Sent: Thursday, June 13, 2013 8:21 AM
To: Pilcher, Ian; Caposino, Paula; Chesler, Ruth A
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Thanks Ian.

We typically do not ask for postmarket agreements for premarket decisions, but this case is special. This 510(k)k is the result of 2 major recalls, and they are instituting a fix that is validated with conflicting data. If they want us to feel like we can make a decision that this device will; be as safe and effective as predicate devices, we need to be assured that some mitigation is in place to address this potential test performance issue. In this case, that mitigation is increased monitoring and a plan for addressing this anticipated problem should it arise. In our response this morning, please let BC know this.

203

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

I agree that 100 is too high. They should begin an investigation if they even see 1 event. I was assuming their threshold for more action was 5 events based on what you said they proposed at first. However, I think something between 5 and 100 is reasonable as well. I wouljd think if they see 20 events (with an "event' being one reported, or one set of reported, incidents confirmed by BC as having been caused by thermally insensitive samples). What does the rest of this group think?

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 8:11 AM
To: Caposino, Paula; Chesler, Ruth A; Lias, Courtney H
Subject: FW: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Beckman's response to our question about how they will proceed if they determine that labs are encountering thermally insensitive samples is below. They have added a third step in which they would stop shipping the product and notify users to stop using it with FDA's agreement. Their threshold for the third option is 100 discrete events per year. This seems like a high number and I would expect them to take this type of action at a much lower threshold, especially since each of these discrete events could contain numerous erroneous results. In the body of the e-mail itself they also state that they are unaware of of any other case where we have required a firm to agree in advance to withdraw a product from the market without going through their normal processes. They also believe that this is not authorized by statute or resolution and that it does not add anything to public health and they ask us to reconsider if such a step is appropriate. They do not include any information on how they will proceed or the steps they will take to remove their current device from the market if their current submission does not show their device to be SE. I don't think we have asked them for this recently, is this something we should be doing considering the timelines and issues with this device?

Please let me know your thoughts on this and how we should respond to this e-mail.

thanks,

an

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a

204

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

incerely,
ɔcott Cundy

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205

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

rom: Cundy, Scott T <STCundy@beckman.com>
ent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity
Attachments: Response to e-mail questions June 10 A2 AI Request (6-12-13) Final.pdf

Hello Ian,

Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

Sincerely,
Scott Cundy

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Thermal

FDA: After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

BEC Response to Question 1

BEC has established an AccuTnI+3 Early Response Team (ERT), to closely monitor the performance of AccuTnI+3 assay for the Access2 instrument for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the AccuTnI+3 assay commercialization for the Access2 instrument, including product performance.

The AccuTnI+3 ERT facilitates real-time cross-functional surveillance of all customer feedback related to the AccuTnI+3 assay. ERT surveillance accelerates investigation into potential product performance issues during the early phase of AccuTnI+3's product release, allowing us to evaluate potential issues before reaching our traditional product escalation thresholds. Therefore, a single report of a potential product performance failure, regardless of the severity and magnitude of the failure, will be rapidly addressed by the ERT. The ERT will investigate all reports of potential "thermal insensitivity" as well as any other unexpected product performance failures.

If thermally insensitive samples are identified and confirmed on the Access2 instrument, BEC will use a risk management approach to determine the appropriate corrective action. For AccuTnI+3 assay, the probability of thermally insensitive samples causing falsely increased or decreased results, resulting in a potentially hazardous situation, has been determined to be Remote according to BEC's risk management process. Since we do not have any historical occurrence rates for this new failure mode, we will use discrete events for determination of the trigger threshold versus an occurrence rate. BEC believes that selecting a specific number of discrete events to trigger action is more conservative than selecting an occurrence rate given the lack of historical information and the large number of tests sold per year (> 28 million). BEC defines the occurrence of 1-4 annual discrete events for the potentially hazardous situation as a Remote occurrence.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s) (see **Table 1-1** below)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 100 (Very high incidence rate)

1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

The actual corrective action(s) depend on the frequency, magnitude, severity, and root cause. Several potential outcomes are possible, and would be driven by the risk assessment and CAPA. Examples of potential corrective actions are identified in **Table 1-1** below:

Table 1-1: Potential Corrective Actions in Event of Failure on the Access2 Instrument

Frequency	Potential Corrective Action
Low incidence (1-4 US annual discrete events)	Customer communication and/or Labeling Change • Technical Bulletin • Important Product Notification • Labeling change (updates to IFU) • Design Change
High incidence ($5 \leq n \leq 99$ US annual discrete events)	All of the above plus… Product CAPA Product Corrective Action escalation Communication to FDA
Very High incidence (≥ 100 US annual discrete events)	All of the above plus… Stop ship product Cease use notification to customers (with FDA agreement)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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The AccuTnI+3 ERT process will rapidly identify and address any product performance issues experienced by customers, including thermally insensitive samples should they occur. This process is directed by and staffed with subject matter experts who have been intimately involved in the development of the thermal algorithm and the AccuTnI+3 reagents, and customer support of the current troponin assay. BEC is committed to this plan to ensure that appropriate action is taken in the event of any AccuTnI+3 performance failure on the Access2 instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Wednesday, June 12, 2013 7:23 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

We will send you the documents you requested tomorrow.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 5:46 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: AccuTnI+3 Access 2 IFU word version (2).docx
Importance: High

Dear Kerrie,
Please see my suggested edits to your IFU. Let me know if you have any questions or if you would like to discuss these suggested edits.
Thanks,
Paula

I will need the 510(k) Summary, Indications for use form, the responses to the questions that I sent you and the IFU tomorrow. I am very sorry that I cannot give you more time.

Please be advised that this email may contain confidential information. If you are not the intended recipient, please notify us by email by replying to the sender and delete this message. The sender disclaims that the content of this email constitutes an offer to enter into, or the acceptance of, any agreement; provided that the foregoing does not invalidate the binding effect of any digital or other electronic reproduction of a manual signature that is included in any attachment.

210

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AccuTnI+3

REF A98143 **FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2**

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy."[12]

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Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV make determination of a significant change more difficult but do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos® 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)

Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin™ 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi, Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

Comment [PVC1]: Please include a statement that patient samples cannot be diluted because this could lead to lower than expected troponin test results. Or something similar.

1. For use on sSerum and lithium heparin plasma ~~are preferred~~ samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]

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- Follow blood collection tube manufacturer's recommendations for centrifugation.
- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty-five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good

Comment [PVC2]: We recommend that you include a recommendation that the user should use commercially available samples near the cut-off. You should consider giving an example (i.e., MORE) or add a statement that the user should call customer service for advice on QC samples to use.

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laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. ~~All or optimal performance,~~ ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). ~~The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]~~

~~Access AccuTnI+3 Result (X) on Access 2~~	~~Report result (X) as:~~
~~X < 0.01 ng/mL (LoD)~~	~~Troponin I not detected; result < 0.01 ng/mL~~
~~0.01 ng/mL (LoD) ≤ X < 0.02 ng/mL (20% CV LoQ)~~	~~X ng/mL, interpret result with caution due to higher assay imprecision~~
~~X ≥ 0.02 ng/mL (20% CV LoQ)~~	~~X ng/mL~~
~~X > ~100 ng/mL (S5 calibrator value)~~	~~> ~100 ng/mL~~

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.

Comment [PVC3]: Please include a limitation that patient samples cannot be diluted because this could result in lower than expected troponin test results. Or something similar.

Comment [PVC4]: Please remove this recommendation. The lower reportable range of troponin should be defined by the LoQ. The reason is that we do not know what the clinical impact may be of reporting troponin values with such high imprecision.

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7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

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Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

Comment [PVC5]: Can you also include that the adjudicators were blinded to the site diagnoses?

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Comment [PVC6]: For your sensitivity, specificity, positive predictive value and negative predictive value, please add how you arrived at your estimate (i.e., 87.4 (221/253)).

Comment [PVC7]: 1.Please make sure that your estimates (and the associated 95% CI) are consistent with the data provided in response to question 3d in the December 14th response (i.e., 95% CI calculated using the Exact Method). There seems to be a mistake in the ≥ 3 to 6 hours for the 0.03 cut-off. While the submission lists the 95% CI as 90.2-97.8, the package insert lists it as 90 to 99. Please correct any discrepancies in the package insert.

Comment [PVC8]: Please include the clinical performance of your device at 0.04 ng/mL and indicate that 0.04 ng/mL is the lowest measured concentration with a %CV (within-lab) <10%. Or something similar. Please make sure to address comments 6 and 7 above. Please include sensitivity, specificity, positive predictive value and negative predictive value.

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94– 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Comment [PVC9]: Please see comments 6, 7 and 8 above.

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

Comment [PVC10]: Please include your definition of no interference (e.g., defined as less than 10% difference between the control sample result and the test sample result).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Substance	Highest Concentration Added	Substance	Highest Concentration Added
Acetaminophen	20 mg/dL	Furosemide	40 mg/dL
Acetylsalicylic Acid	65 mg/dL	Hemoglobin	5 mg/mL
Allopurinol	40 mg/dL	Human Serum Albumin	6000 mg/dL
Ambroxol	40 mg/dL	Ibuprofen	50 mg/dL
Ampicillin	5 mg/dL	Low MW Heparin	28.8 U/mL
Ascorbic Acid	6 mg/dL	Methyldopa	2.5 mg/dL
Atenolol	1 mg/dL	Nifedipine	60 µg/mL
Bilirubin (conjugated)	40 mg/dL	Nitrofurantoin	6.4 mg/dL
Bilirubin (unconjugated)	40 mg/dL	Nystatin	2.15 mg/dL
Biotin	290 ng/mL	Oxytetracycline	24 mg/dL
Caffeine	10 mg/dL	Phenytoin	10 mg/dL
Captopril	5 mg/dL	Propranolol	500 µg/mL
Cinnarizine	40 mg/dL	Quinidine	2 mg/dL
Cocaine	2 mg/dL	Simvastatin	20 µg/mL
Diclofenac	5 mg/dL	Theophylline	25 mg/dL
Digoxin	200 ng/mL	Triglycerides	3000 mg/dL
Dopamine	30 mg/dL	Trimethoprim	7.5 mg/dL
Erythromycin	20 mg/dL	Verapamil	16 mg/dL
Fibrinogen	1000 mg/dL	Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

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Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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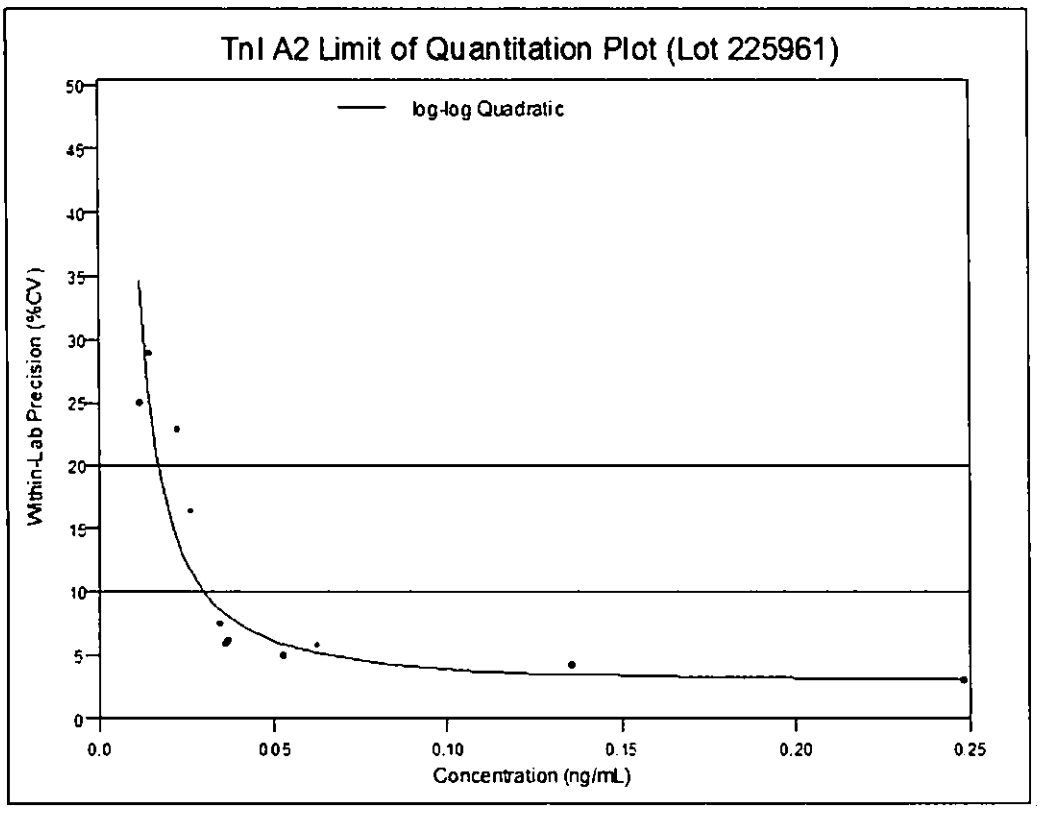

Comment [PVC11]: We recommend that you remove this graph. If you want to include a representative limit of quantitation plot, we recommend that you include the graph "Run temp 28 degrees" (Figure 13-5) from the June 4th response under "Third AI letter". The reason for this is that the performance at 28 degrees is more representative of the overall imprecision of your device.

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223

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Wednesday, June 12, 2013 6:01 PM
To: Caposino, Paula; Kerrie Oetter (koetter@live.com)
Cc: Cundy, Scott T
Subject: RE: k121214 suggested edits to Intended Use Statement

Dear Paula,

I will implement the suggested edits.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 4:52 PM
To: Kerrie Oetter (koetter@live.com); Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: k121214 suggested edits to Intended Use Statement

Dear Kerrie,
Please find enclosed my suggested edits to the Indication for Use Form:

Device name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrator for use on the Access 2 Immunoassay System

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Please make the following changes: Concurrence of CDRH, Office of In Vitro ~~Devices~~ Diagnostics and Radiological Health (OIR)
Division Sign-Off
Office of In Vitro ~~Devices~~ Diagnostics and Radiological Health ~~Evaluation and Safety~~

Thanks,
Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer

224

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food and Drug Administration
CDRH, OIR, DCTD
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Caposino, Paula

From: De, Arkendra
Sent: Wednesday, June 12, 2013 5:29 PM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Revised Text

I think that their method of analysis underestimates the variability since they are averaging.
This might be why their standard deviation results are lower than FDA's results.
I recommend the following be sent to the sponsor, in which they revise their calculations for the precision study.

To the sponsor:
1. You state in your revision to the answer to question 1 that you used an ANOVA model with only run as an independent variable for each temperature-instrument combination.
Results were averaged for each instrument-temperature combination to yield the within-lab standard deviation. Averaging results in this manner could underestimate the variability in results, as depicted in your response dated June 10, 2013 to question 2. We recommend that you report and calculate the within-lab standard deviation by computing the standard deviation for all results combined across all temperature-instrument combinations, separately for each sample, so that the variability is not underestimated. Below are FDA's results using this recommendation.

Sample ID	Mean	Within-Lab Standard Deviation	%CV
1	0.011	0.0042	38.181818
2	0.014	0.0051	36.428571
3	0.023	0.0059	25.652174
4	0.026	0.0054	20.769231
5	0.037	0.0032	8.648649
6	0.038	0.0034	8.947368
7	0.053	0.0036	6.792453
8	0.063	0.0052	8.253968
9	0.138	0.0081	5.869565
10	0.254	0.0144	5.669291
11	0.036	0.0036	10.000000

From: Caposino, Paula
Sent: Wednesday, June 12, 2013 1:46 PM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: FW: Revised Text

FYI, they updated the response to this question. Does this change anything?

Note to File: This was not communicated to the sponsor. Arkendra analysed the data and we realized that the sponsor's estimates are O.K. See Arkendra's June 13th, 2013 email.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOIASTATUS@fda.hhs.gov or 301-796-8118

226

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Wednesday, June 12, 2013 3:55 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Beckman Coulter response to k121214 June 7 AI Request
Attachments: k121214 Access AccuTnI+3 Access 2 Labels.pdf; 510(k) Summary AccuTnI+3 Access 2.doc; AccuTnI+3 Access 2 IFU word version.docx

Importance: High

Dear Paula,

I have attached the word version of our 510(k) Summary and IFU (please note that the word version of IFU will be look different – formatting and graphics have changed some when it was transferred from an Adobe FrameMaker to word version). I have also attached the PDF version of our labels. We are unable to changes our labels to word files. Please just annotate any changes on the PDF copy.

The trade names used for the product are Access AccuTnI+3 Reagent , Access AccuTnI+3 Calibrators and Access 2 Immunoassay System. The product name is the Access AccuTnI+3 Assay. It is a little complicated, these three individual items do not function on their own, but together with a patient sample, wash buffer and substrate, the Assay as a whole is culminated. With this culmination, ability to deliver the patient result is achieved, which is ultimately the goal. There are times when it is necessary to refer to the Assay as a whole, and times when it is important to refer to the components individually. We cannot always use Access AccuTnI+3 Reagents or Access AccuTnI+3 Assay exclusively, as they do mean different things.

Let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 10:29 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: Beckman Coulter response to k121214 June 7 AI Request
Importance: High

Good morning:
I will need some help today getting some clarification and additional details. To get this started, can you please clarify if your trade name is Access AccuTnI+3 Reagent or the Access AccuTnI+3 Assay. We recommend that you change wherever you list the device as Access AccuTnI+3 Assay to Access AccuTnI+3 Reagent (i.e., (510(k) Summary and IFU))or vice versa. We just need this to be consistent. If you could send me a word version of your IFU and your 510(k) Summary, I can send you back a list of the changes we recommend to these documents.
Also, would send me a word version of your labeling? We have some changes we would like to recommend and I think it may be best to have it as a Word File.

227

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Let me know if you agree.
Thanks,
Paula

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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is k121214

Submitted By:

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1142
Fax: (952) 368-7610

Contact Person:

Kerrie Oetter
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-7858
Fax: (952) 368-7610

Date Prepared:

June 12, 2013

Device Name:

Proprietary / Trade Name: Access AccuTnI+3 Reagent and Calibrator for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215
Classification Product Code: MMI
Subsequent Product Code: JIT

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160
Classification Product Code: JJE

Predicate Devices:

The Access AccuTnI+3 reagent and calibrators claim substantial equivalence to the TnI-Ultra™ Assay and Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Device Description:

The Access AccuTnI+3 reagents, AccuTnI+3 calibrators and the Access 2 Immunoassay System compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI+3 reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

Intended Use:

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI+3 reagent and calibrators and the predicate device, ADVIA Centaur® TnI-Ultra™ reagent and calibrators, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Similarities between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Calibrators
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same

Differences between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Calibrators
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2 Immunoassay System
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized: high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.02 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.9 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.042 ng/mL	Total CV of ≤8% at concentrations >0.075 ng/mL. SD ≤0.006 at concentrations ≤0.075 ng/mL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Calibrators
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction. The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 System K922823/A007	New Device Access 2 System
Indication for Use	The Access 2 Immunoassay system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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AccuTnI+3

REF A98143 **FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2**

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy."[12]

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Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)

Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

   Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.

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- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access 2
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's

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instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]

Access AccuTnI+3 Result (X) on Access 2	Report result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result < 0.01 ng/mL
0.01 ng/mL (LoD) ≤ X < 0.02 ng/mL (20% CV LoQ)	X ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% CV LoQ)	X ng/mL
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.

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8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate

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sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94– 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added	Substance	Highest Concentration Added
Acetaminophen	20 mg/dL	Furosemide	40 mg/dL
Acetylsalicylic Acid	65 mg/dL	Hemoglobin	5 mg/mL
Allopurinol	40 mg/dL	Human Serum Albumin	6000 mg/dL
Ambroxol	40 mg/dL	Ibuprofen	50 mg/dL
Ampicillin	5 mg/dL	Low MW Heparin	28.8 U/mL
Ascorbic Acid	6 mg/dL	Methyldopa	2.5 mg/dL
Atenolol	1 mg/dL	Nifedipine	60 µg/mL
Bilirubin (conjugated)	40 mg/dL	Nitrofurantoin	6.4 mg/dL
Bilirubin (unconjugated)	40 mg/dL	Nystatin	2.15 mg/dL
Biotin	290 ng/mL	Oxytetracycline	24 mg/dL
Caffeine	10 mg/dL	Phenytoin	10 mg/dL
Captopril	5 mg/dL	Propranolol	500 µg/mL
Cinnarizine	40 mg/dL	Quinidine	2 mg/dL
Cocaine	2 mg/dL	Simvastatin	20 µg/mL
Diclofenac	5 mg/dL	Theophylline	25 mg/dL
Digoxin	200 ng/mL	Triglycerides	3000 mg/dL
Dopamine	30 mg/dL	Trimethoprim	7.5 mg/dL
Erythromycin	20 mg/dL	Verapamil	16 mg/dL
Fibrinogen	1000 mg/dL	Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.

Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

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Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

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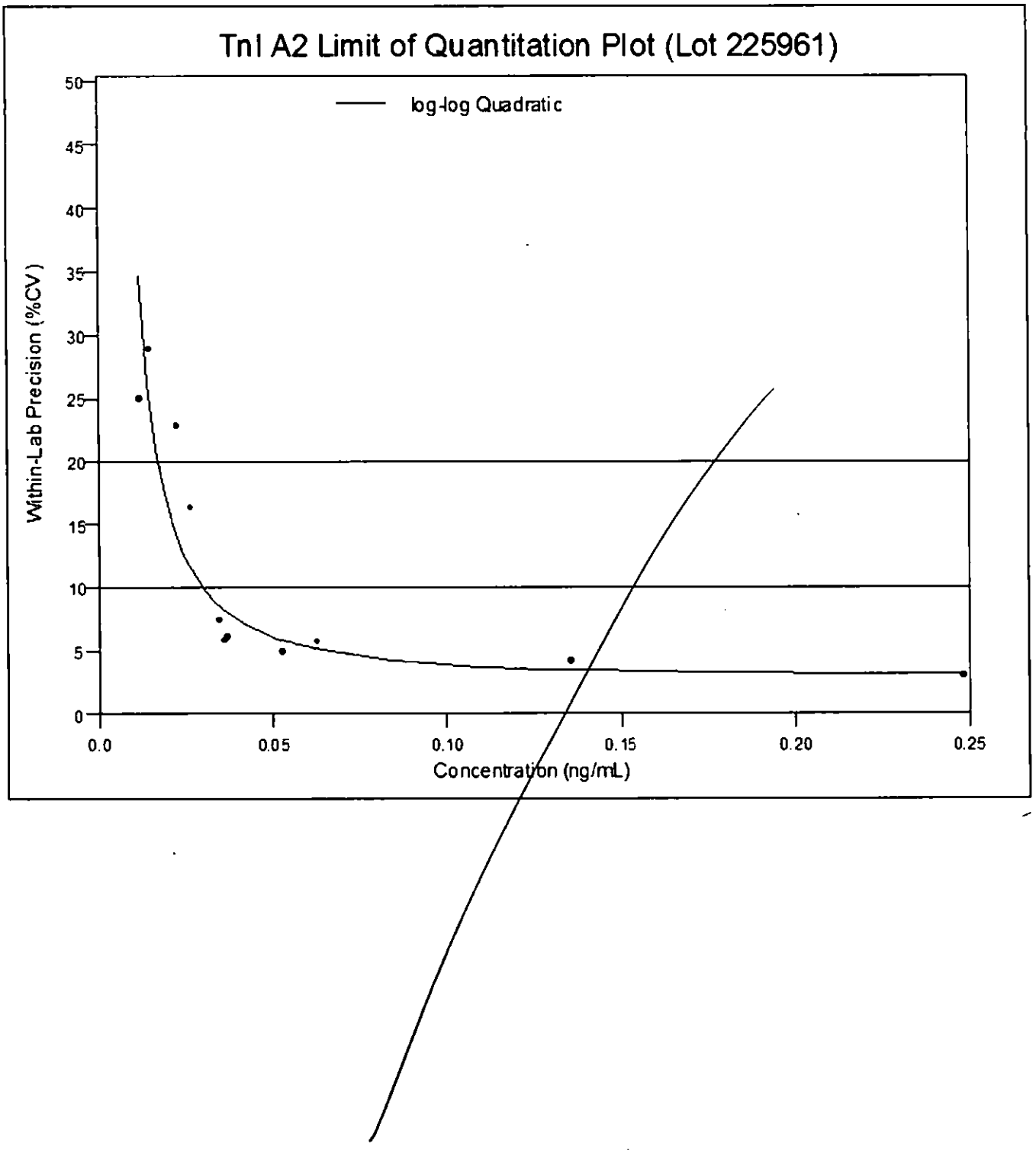

246

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AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)

Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

247

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

248

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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249

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Wednesday, June 12, 2013 1:19 PM
To: Caposino, Paula
Subject: RE: Revised Text

Great.

Thanks.

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 12:19 PM
To: Cundy, Scott T
Subject: RE: Revised Text

Dear Scott,
No need. I can add this to the file.
Thanks
Paula

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Wednesday, June 12, 2013 1:17 PM
To: Caposino, Paula
Subject: Revised Text

Hello Paula,

Yesterday we sent you a response to your LoQ question. I need to revise the text slightly. Sorry for the confusion. The data does not change and the results do not change. The description of our analysis changes slightly. I have attached our revised text and will plan to submit it to the DMC.

Thank you,
Scott

1. **Limit of quantitation (LoQ)**

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Wednesday, June 12, 2013 1:17 PM
To: Caposino, Paula
Subject: Revised Text
Attachments: Response to June 7- Q1 revision.docx

Hello Paula,

Yesterday we sent you a response to your LoQ question. I need to revise the text slightly. Sorry for the confusion. The data does not change and the results do not change. The description of our analysis changes slightly. I have attached our revised text and will plan to submit it to the DMC.

Thank you,
Scott

1. **Limit of quantitation (LoQ)**

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BECKMAN COULTER.

Responses to FDA's June 7, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Limit of quantitation (LoQ)

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

BEC Response to Question 1

Within each run temperature, three instruments were each calibrated at three different temperatures, providing nine testing scenarios. The three days and two runs per day for each testing scenario were seen as six runs with 10 replicates for each run (60 total replicates). A simple analysis of variance (ANOVA) with troponin in ng/mL as the dependent variable and run as the independent variable was performed using a generalized linear model (EP15-A2) to provide within-run and between-run standard deviations with their combination being within-laboratory standard deviations (SD).

For each sample, the within-laboratory variances and mean values from all nine scenarios were averaged. The coefficient of variation (CV) was computed for each sample by first taking the square root of its within-laboratory variance to obtain standard deviation and then dividing by the average mean value. The resultant precision profile analysis using the mean and %CV for each sample provided an estimate of 10% LoQ at 0.04 ng/mL and 20% LoQ at 0.02 ng/mL for troponin in the same manner as Appendix D in CLSI EP17-A2.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

rom: Cundy, Scott T <STCundy@beckman.com>
ent: Wednesday, June 12, 2013 12:10 PM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC's Proposed Action Plan in the Event of a Thermally Insensitive Sample
Attachments: K121214 response to e-mail questions June 10 A2 AI Request.pdf

Hello Ian,

Attached is BEC's proposed action plan in the event that we encounter a thermally insensitive sample. The report is due to the FDA today by 2 PM EST. I'm wondering if you might be open to reviewing the document, and then giving me a quick call to discuss. I want to be sure that we are satisfying the agency's request. I thought it might be useful if we talked before it is due so that if I need to add something, I would still have time.

Please let me know your thoughts.

Thank you so much,
Scott

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Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Thermal

FDA: After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

BEC Response to Question 1

BEC has established an AccuTnI+3 Early Response Team (ERT), to closely monitor the performance of AccuTnI+3 for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the AccuTnI+3 assay commercialization, including product performance.

The AccuTnI+3 ERT facilitates real-time cross-functional surveillance of all customer feedback related to the AccuTnI+3 assay. ERT surveillance accelerates investigation into potential product performance issues during the early phase of AccuTnI+3's product release, allowing us to evaluate potential issues before reaching our traditional product escalation thresholds. Therefore, a single report of a potential product performance failure, regardless of the severity and magnitude of the failure, will be rapidly addressed by the ERT. The ERT will investigate all reports of potential "thermal insensitivity" as well as any other unexpected product performance failures.

If thermally insensitive samples are identified and confirmed, BEC will use a risk management approach to determine the appropriate corrective action. For AccuTnI+3, the probability of thermally insensitive samples causing falsely increased or decreased results, resulting in a potentially hazardous situation, has been determined to be Remote according to BEC's risk management process. Since we do not have any historical occurrence rates for this new failure mode, we will use discrete events for determination of the trigger threshold versus an occurrence rate. BEC believes that selecting a specific number of discrete events to trigger action is more conservative than selecting an occurrence rate given the lack of historical information and the large number of tests sold per year (> 28 million). BEC defines the occurrence of 1-4 annual discrete events for the potentially hazardous situation as a Remote occurrence.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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If annual discrete events = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s) (see **Table 1-1** below)
4. Continue post-launch surveillance

If annual discrete events ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased result(s) where the increase or decrease is proven to be caused by inappropriate adjustment of the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

The actual corrective action(s) depend on the frequency, magnitude, severity, and root cause. Several potential outcomes are possible, and would be driven by the risk assessment and CAPA. Examples of potential corrective actions are identified in **Table 1-1** below:

Table 1-1: Potential Corrective Actions in Event of Failure

Frequency	Potential Corrective Action
Low incidence (1-4 discrete events)	Customer communication and/or Labeling Change • Technical Bulletin • Important Product Notification • Labeling change (updates to IFU) • Design Change
High incidence (≥ 5 discrete events)	All of the above plus… Product CAPA Product Corrective Action escalation Communication to FDA

The AccuTnI+3 ERT process will rapidly identify and address any product performance issues experienced by customers, including thermally insensitive samples should they occur. This process is directed by and staffed with subject matter experts who have been intimately involved in the development of the thermal algorithm and the AccuTnI+3 reagents, and customer support of the current troponin assay. BEC is committed to this plan to ensure that appropriate action is taken in the event of any AccuTnI+3 performance failure.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 2: Limit of quantitation (LoQ)

FDA: Please provide an explanation for the difference in the performance of sample 4 depending on the instrument used (please refer to FDA's Calculation of Within-Lab Standard Deviation and %CV for Each Instrument). We are concerned that the %CV for this sample doubled (from 15% to 30%) depending on the instrument that was used. Again, please provide this information by Wednesday June 12, 2013 at 2:00 P.M.

FDA's Calculations of Within-Lab Standard Deviation and %CV for Each Instrument

Instrument	Sample ID	Mean	SD	%CV
402603	4	0.025	0.007	30%
502884	4	0.027	0.005	19%
507310	4	0.026	0.004	15%

BEC Response to Question 2

BEC calculations of within-laboratory standard deviation yield slightly different, but similar values to those calculated by the Agency (See **Table 2-1**):

Table 2-1: Within-Lab Standard Deviation and %CV of Sample 4 by Instrument

Instrument	Sample ID	Mean	SD	%CV
402603	4	0.025	0.0067	26%
502884	4	0.027	0.0047	18%
507310	4	0.026	0.0038	15%

Imprecision estimates are subject to variability much like individual replicates. A distribution of imprecision measurements is expected when the same sample is evaluated on numerous occasions and under multiple conditions. The result for Instrument 402603 above can likely be attributed to the random variability associated with imprecision estimates. This random variability cannot be distinguished from systematic variability associated with a particular variable based on this data alone. Other samples in the Limit of Quantitation (LoQ) study demonstrate lower or equivalent imprecision on Instrument 402603 when compared to the other two instruments (see **Table 2-2** for two examples), further supporting the hypothesis of random rather than systematic differences in imprecision.

Table 2-2: Within-Lab Standard Deviation and %CV of Samples 2 and 11 by Instrument

Instrument	Sample ID	Mean	SD	%CV
402603	2	0.014	0.0033	24%
502884	2	0.016	0.0050	31%
507310	2	0.014	0.0035	26%
402603	11	0.037	0.0025	7%
502884	11	0.035	0.0029	8%
507310	11	0.034	0.0023	7%

Creating a precision profile using multiple samples in the derivation of LoQ provides a robust estimation of imprecision at specified concentrations while reducing the impact of random variability observed for individual samples. When results for all samples in the Limit of Quantitation (LoQ) study are evaluated, rather than a single sample on a single instrument, the precision profile approach as specified in Appendix D of CLSI EP17-A2 yields a 20% CV LoQ of 0.02 ng/mL. This same conclusion is reached regardless of whether the study is evaluated instrument by instrument, reagent lot by reagent lot, or run temperature by run temperature.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Callaghan, Jim
Sent: Wednesday, June 12, 2013 7:52 AM
To: Caposino, Paula
Subject: RE: Information for DS for instrument that we are getting ready to clear.

I would only put in the stuff in bold plus what you have under Systems Descriptions. You should also include the Troponin description

Jim

From: Caposino, Paula
Sent: Tuesday, June 11, 2013 6:55 PM
To: Callaghan, Jim
Subject: Information for DS for instrument that we are getting ready to clear.

Hi Jim,
I am preparing the DS for the Access 2 Immunoassay System that will most likely be cleared with troponin from Beckman Coulter. I was hoping you would look at this information that I want to put in the DS for the analyzer. Is this too much? Is it not enough? Let me know if I am in the ballpark. Thanks.
Paula

Device description:

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into the system. The APF contains all assay specific parameters used to process a particular assay including:

- Identification of reagents used to process the assay
- The sequence and volumes of the sample and reagent additions
- Mixing parameters
- Incubation times
- Math model used to convert the measured response to a reportable result
- Calibration information
- Thermal algorithm

The major Access 2 Immunoassay System components which execute all system processing, control and interface functions are listed below:

- Carousel Module
- Pipettor Module
- Analytical Module
- Fluidic Module
- Electronic/Systems Computer
- Peripheral Module

Systems Descriptions:

259

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1. Modes of Operation:
   Micro computer controlled analyzer with random and continuous access.

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
   Yes __X___ or No ____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
   Yes _____ or No __X__

2. Software:
   FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
   Yes __X___ or No _____

3. Specimen Identification:
   Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
   Instruction on sample handling is provided in the reagent labeling.

5. Calibration:
   An active calibration curve is required for all tests. For the Access AccuTnI assay, calibration is required every 56 days.

6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

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260

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Monday, June 10, 2013 2:47 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Beckman Coulter response to k121214 June 7 AI Request

Importance: High

Dear Paula,

Please call – 4pm Eastern Time

Toll-free dial-in number (U.S. and Canada):
(866) 548-3459

Conference code:
276 553 7316

Beckman Coulter Employees that will be on the teleconference:

Scott Cundy, Vice President Regulatory Affairs and Quality

Kerrie Oetter, Senior Regulatory Affairs

Kathy Horsfall, Senior Program Manager

Corey Carlson, Development Manager

Eric Hjelm, Staff Application Scientist

Marion Navratil – Senior Manager Development

Thanks,
Kerrie Oetter

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, June 10, 2013 12:59 PM
To: Cundy, Scott T
Cc: Oetter, Kerrie S
Subject: FW: Beckman Coulter response to k121214 June 7 AI Request
Importance: High

Dear Scott,

Thank you for the information that you provided to me this morning.

After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency

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needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

We would also like to schedule a teleconference with you for today to discuss this request. Let me know what time you are available.

Thank you very much,

Paula

P.S., I will follow up this email with a question regarding your LoQ analyses from our Statisticians.

262

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Caposino, Paula

From: De, Arkendra
Sent: Monday, June 10, 2013 2:00 PM
To: Caposino, Paula
Subject: RE: Follow up question for Beckman. Does this get to the point?

Yes, it gets to the point. Looks good

Arkendra

From: Caposino, Paula
Sent: Monday, June 10, 2013 1:58 PM
To: De, Arkendra
Subject: Follow up question for Beckman. Does this get to the point?

Dear Kerrie,

Please provide an explanation for the difference in the performance of sample 4 depending on the instrument used (please refer to FDA's Calculation of Within-Lab Standard Deviation and %CV for Each Instrument). We are concerned that the %CV for this sample doubled (from 15% to 30%) depending on the instrument that was used. Again, please provide this information by Wednesday June 12, 2013 at 2:00 P.M.

FDA's Calculations of Within-Lab Standard Deviation and %CV for Each Instrument

Instrument	Sample id	Mean	SD	%CV
402603	4	0.025	0.007	30%
502884	4	0.027	0.005	19%
507310	4	0.026	0.004	15%

Thank you in advance for your response.

Regards,

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
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Silver Spring, MD 20993
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Caposino, Paula

From: Pilcher, Ian
Sent: Monday, June 10, 2013 12:48 PM
To: Caposino, Paula; Chesler, Ruth A
Subject: RE: Corrective Action Plan request from Beckman--Please read for adequacy????

looks good to me.

Ian

From: Caposino, Paula
Sent: Monday, June 10, 2013 12:40 PM
To: Pilcher, Ian; Chesler, Ruth A
Subject: Corrective Action Plan request from Beckman--Please read for adequacy????
Importance: High

Dear Scott and Kerrie,

Thank you for the information that you provided to me this morning.

After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

We would also like to schedule a teleconference with you for today to discuss this request. Let me know what time you are available.

Thank you very much,

Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160

265

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Caposino, Paula

From: De, Arkendra
Sent: Monday, June 10, 2013 10:56 AM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse
Attachments: FDA Plasma Calculations for K121214.doc

Thanks Paula. I just saw that Beckman sent in the response for the questions we had on Friday of last week. Attached are calculations that I did using only the plasma measurements.

A few things I noticed:
1. Page 28 of the Sponsor's May 3, 2013 response doesn't make sense to me. The %CV listed in table 13-3 on page 28 doesn't match the calculated results.
What I mean is that when dividing the standard deviation by the mean and multiplying by 100, using the numbers in the table, the %CV result is not the same as the %CVs depicted in the table.
2. The calculated results from me differs from the sponsor's table 13-3 on page 28 (referring to same response as number 1). As it turns out, the sponsor did something different (haven't gotten a chance to look at it in detail).
3. There are statistically significant differences in the variance when comparing across instruments at 28 C run temperature. These are in the attachment.

Arkendra

From: Caposino, Paula
Sent: Monday, June 10, 2013 9:12 AM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Sorry Arkendra,
I just got this. The Q2 is likely the plasma measurements and the Q6 is in serum.
Thanks,
Paula

We could just focus on plasma.

267

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FDA's Calculations of Within-Lab Standard Deviation and %CV for Each Instrument

Used only plasma data for all calculations

Instrument 402603

Sample ID	Mean	SD (across instruments, sites, temperature, runs, days, replicates)	%CV
1	0.011	0.005	45%
2	0.014	0.005	36%
3	0.023	0.006	26%
4	0.025	0.007	30%
5	0.038	0.003	7.89%
6	0.039	0.003	7.69%
7	0.053	0.003	5.66%
8	0.064	0.006	9.38%
9	0.142	0.007	4.93%
10	0.264	0.0164	6.21%
11	0.037	0.003	8.11%

Instrument 502884

Sample ID	Mean	SD (across instruments, sites, temperature, runs, days, replicates)	%CV
1	0.013	0.004	31%
2	0.016	0.005	31%
3	0.023	0.006	26%
4	0.027	0.005	19%
5	0.037	0.003	8.11%
6	0.037	0.003	8.11%
7	0.053	0.003	5.66%
8	0.062	0.005	8.06%
9	0.134	0.007	5.22%
10	0.247	0.009	3.64%
11	0.035	0.003	8.57%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Instrument 507310

Sample ID	Mean	SD (across instruments, sites, temperature, runs, days, replicates)	%CV
1	0.011	0.004	36%
2	0.013	0.004	31%
3	0.022	0.006	27%
4	0.026	0.004	15%
5	0.036	0.003	8.33%
6	0.037	0.003	8.11%
7	0.053	0.004	7.55%
8	0.063	0.005	7.94%
9	0.138	0.007	5.07%
10	0.250	0.010	4.00%
11	0.034	0.003	8.82%

Instrument/Temperature Combination Within-Lab Standard Deviations

	Instrument 402603, Run Temp 28 C Within-Lab Standard Deviaiton	Instrument 502884, Run Temp 28C Within-Lab Standard Deviaiton	Instrument 507310, Run Temp 28 C Within-Lab Standard Deviaiton
Sample 1*	0.002	0.005	0.004
Sample 2*	0.004	0.008	0.005
Sample 3	0.008	0.007	0.008
Sample 4*	0.009	0.007	0.005
Sample 5	0.003	0.003	0.003
Sample 6	0.003	0.003	0.003
Sample 7*	0.002	0.003	0.004
Sample 8	0.004	0.004	0.004
Sample	0.006	0.008	0.005

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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9*			
Sample 10*	0.015	0.007	0.0096
Sample 11	0.002	0.003	0.003

*Indicates that the variance of these samples differs across instruments in a strongly statistically significant sense (using Bartlett's test for testing equality of variances)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Kerrie Oetter <koetter@live.com>
Sent: Monday, June 10, 2013 10:21 AM
To: Caposino, Paula
Cc: ksoetter@beckman.com; stcundy@live.com
Subject: Beckman Coulter response to k121214 June 7 AI Request
Attachments: k121214 response to June 7 AI request.pdf; Appendix 1.pdf

Dear Paula,

Attached is our response to your request dated June 7, 2013, for k121214. You will find the response and revised IFU attached. I am sending the response through my personal e-mail, since the Beckman Coulter Outlook is currently out of service.

Please let me know if you have any questions.

Thanks,
Kerrie Oetter
ksoetter@beckman.com / 952-368-7858

271

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER.

Responses to FDA's June 7, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Limit of quantitation (LoQ)

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

BEC Response to Question 1

Within each run temperature, three instruments were each calibrated at three different temperatures, providing nine testing scenarios. The data from each scenario's set of 60 replicates (3 days of 2 runs per day with 10 replicates each run) was analyzed using a general linear model as specified in CLSI EP5-A2. This nested analysis of variance (ANOVA) had troponin in ng/mL as the dependent variable and the following independent variables: day and run nested within day. The resultant run and day variances were added together to obtain between-run variance. The residual variance (within-run) was added to the between-run variance to obtain the within-laboratory variance.

For each sample, the within-laboratory variances and mean values from all nine scenarios were averaged. The coefficient of variation (CV) was computed for each sample by first taking the square root of its within-laboratory variance to obtain standard deviation and then dividing by the average mean value. The resultant precision profile analysis using the mean and %CV for each sample provided an estimate of 10% LoQ at 0.04 ng/mL and 20% LoQ at 0.02 ng/mL for troponin in the same manner as Appendix D in CLSI EP17-A2.

Question 2: Limit of quantitation (LoQ)

FDA: Can you please provide the results of the regression analysis for the study comparing lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort in singlicate excluding all samples under the LoQ of your device?

BEC Response to Question 2.

The Pivotal Trial Cohort data have been analyzed following exclusion of samples with troponin values below AccuTnI+3 assay's LoQ; the following exclusion of those samples, is provided in Table 2-1 below:

Table 2-1: AccuTnI+3 Access 2, Serum vs Plasma, Passing Bablok

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 - 20	96	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 3: Field Effectiveness Study

FDA: Can you explain why the results of sample MORE 1 provided in table 2-3 "More 1 Precision Results from the Field Effectiveness Study" from site S on lot 2 do not appear to support your current LoQ claim? Specifically, the mean result obtained by the site based on a sample size of 40 was 0.022 ng/mL with a %CV of 29.1. We are concerned that these data demonstrate that at 0.02 ng/mL, your device may not consistently provide results with the claimed %CV of less than 20%. Please provide an explanation for these results.

BEC Response to Question 3

A number of complex, well-controlled studies were conducted to establish our LoQ claims including those described in the response to question 1 above. These studies used patient samples as recommended in EP17-A2. Results from the analyses of the studies carried out in accordance with EP17-A2 demonstrate that the 20% LoQ is 0.02 ng/mL.

The External Field Effectiveness study was designed to evaluate the precision of three AccuTnI+3 reagent lots in multiple laboratories over multiple days/runs, in the hands of clinical laboratory technologists. Results were intended to provide additional confidence that the final AccuTnI+3 product in its entirety—including thermal algorithm, system software, assay protocol files, etc.—performs properly on fielded instruments.

The samples used in the Field Effectiveness study were commercial quality controls (QC) that are intended to reflect the behavior of natural patient samples and thus yield results that are predictive of results from patient specimens. We used commercial QC in the Field Effectiveness study because our customers would typically use these kinds of controls to assess the assay's precision performance and to detect performance issues on a daily basis before testing patient specimens. By using commercial QC in the Field Effectiveness study, we evaluated the performance of the device as our customers would and as it is intended to be used in the field.

Our analysis of results from this study showed that the precision acceptance criteria were met for each of the six QC samples tested at five external laboratories using three lots of reagents. The current question focuses on results provided in Table 2-3 of our most recent supplemental response. That table, reproduced below, contains the MORE QC level 1 results from the Field Effectiveness study where each site performed a multiday analysis of precision with each of three reagent lots, yielding fifteen sets of results including mean TnI concentration, % CV and standard deviation.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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As shown in Table 2-3, 12 of the 15 mean TnI concentrations for the MORE 1 QC sample fall below 0.02 ng/mL, indicating that the actual concentration of the specimen is below 0.02 ng/mL.

Table 3-1: MORE 1 Precision Results from the Field Effectiveness Study

Site	Sample	Lot	n	Concentration (ng/mL)	CV	SD
U	MORE 1	1	40	**0.016**	20.6%	0.0033
A	MORE 1	1	80	0.020	20.5%	0.0041
S	MORE 1	1	40	**0.011**	52.7%	0.0058
Q	MORE 1	1	40	0.023	5.7%	0.0013
E	MORE 1	1	36	**0.016**	31.3%	0.0050
U	MORE 1	2	40	**0.013**	20.8%	0.0027
A	MORE 1	2	62	**0.010**	28.0%	0.0028
S	MORE 1	2	40	0.022	29.1%	0.0064
Q	MORE 1	2	40	**0.018**	14.4%	0.0026
E	MORE 1	2	36	**0.013**	38.5%	0.0050
U	MORE 1	3	40	**0.010**	16.0%	0.0016
A	MORE 1	3	62	**0.010**	32.0%	0.0032
S	MORE 1	3	40	**0.010**	45.0%	0.0045
Q	MORE 1	3	40	**0.017**	12.9%	0.0022
E	MORE 1	3	36	**0.010**	35.0%	0.0035

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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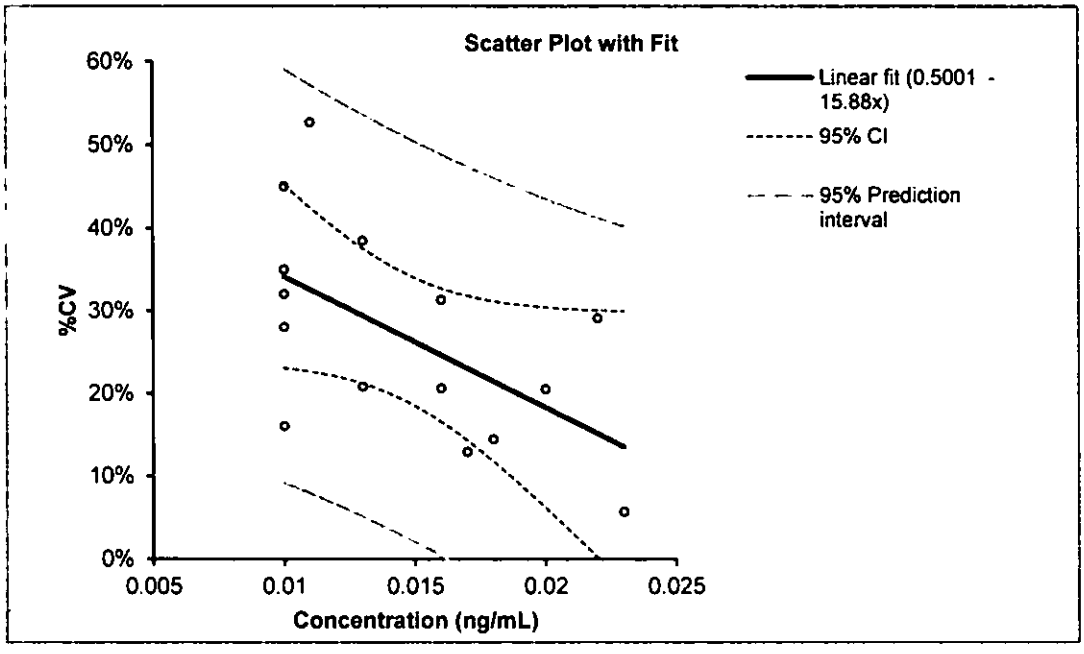
We also provided findings from a precision profile analysis based on CV using all of the MORE I data in the most recent supplemental response. It is important to note that by using a precision profile approach as specified in Appendix D of CLSI EP17-A2 a regression analysis shows a significant relationship between concentration and %CV (p=0.025). This analysis takes into account information from all of the observations rather than just a single observation. Results from the precision profile (Figure 2-1 shown below) showed a calculated precision of 18.3% CV at 0.02 ng/mL.

Figure 3-1: Precision Profile



These data support our conclusion that the 20% LoQ of the AccuTnI+3 assay on the Access 2 is 0.02 ng/mL. In light of the extensive evidence we have provided based on results from native patient samples and commercial controls, results from the one data set in question can be attributed to random variation.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER.

Question 4: Linearity

FDA: Your acceptance criteria for samples with troponin concentrations less than 0.075 ng/mL for maximum deviation from linearity is 0.012 ng/mL. Meanwhile you state "in the new low-range linearity studies, the maximum deviation from linearity was 1%." Your current acceptance criterion for linearity for samples less than 0.075 ng/mL is unacceptable broad (allowable nonlinearity of ± 60% at 0.02 ng/mL, ± 40% at 0.03 ng/mL and ± 30% at 0.04 ng/mL). Based on your data (maximum observed non-linearity is 1% in the new low-range linearity studies) you can tighten this criteria. Please tighten the criteria for allowable maximum deviation from linearity for samples less than 0.075 ng/mL (We recommend no more than +-15%).

BEC Response to Question 4

The criteria will be tightened to a maximum allowable deviation from linearity of ≤15% across the entire assay range. The product instruction for use (IFU) has been updated to reflect these tightened criteria. A copy of the revised Instructions for Use (IFU) is attached in Appendix 1.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 1: Device labeling (Instructions for Use, IFU)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[13] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.

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- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access 2
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since

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obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]

Access AccuTnI+3 Result (X) on Access 2	Report result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result < 0.01 ng/mL
0.01 ng/mL (LoD) ≤ X < 0.02 ng/mL (20% CV LoQ)	X ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% CV LoQ)	X ng/mL
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

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Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

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Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94 – 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

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In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

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Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

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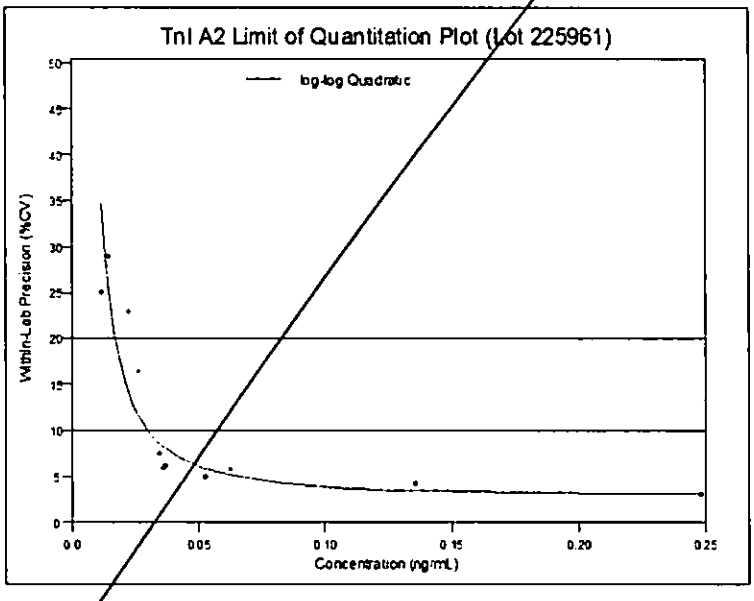
Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: De, Arkendra
Sent: Friday, June 07, 2013 6:51 PM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Paula,

As I was looking at the Excel file, I noticed that there are two tabs in the spreadsheet related to LoQ.
One of them is "Q2 Lmts of Detection (LoD-LoQ)" , and the other is "Q6 Matrix Comp (Serum LoD-LoQ)".
Could you tell me what these refer to and what the difference is between these two?
Should I use both tabs when analyzing the data?

Thanks,
Arkendra

From: Caposino, Paula
Sent: Friday, June 07, 2013 11:02 AM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Perfect. I'll talk to you then.

I would like to confirm that the sponsor's power function model by run temperature (just 28 degrees) is correct for both serum and plasma.

From: De, Arkendra
Sent: Friday, June 07, 2013 11:00 AM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Paula,

Kristen and I talked earlier, and we were thinking of meeting with you at 1:30 pm today.
Does that work for you? We also were thinking of gathering at Kristen's office (for those in White Oak) for the meeting.
Please let me know.

Thanks,
Arkendra

From: Meier, Kristen L.
Sent: Friday, June 07, 2013 10:40 AM
To: Caposino, Paula
Cc: De, Arkendra
Subject: RE: Beckman Troponin REsponse

293

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Thanks Paula – when Arkendra starts working we can see what time works for him.
Arkendra – one thing we want to do with the Excel file is just get a better understanding of the study design they used...

Kristen

From: Caposino, Paula
Sent: Friday, June 07, 2013 10:31 AM
To: Meier, Kristen L.; De, Arkendra
Subject: RE: Beckman Troponin REsponse

Here it is.
Thanks.
I'm free for the rest of the day so let me know when you want me to come down.
Paula

From: Meier, Kristen L.
Sent: Friday, June 07, 2013 10:04 AM
To: Caposino, Paula; De, Arkendra
Subject: RE: Beckman Troponin REsponse

Hi Paula – if you can email the excel file that would be a huge help. I have a sponsor telecom 11-12 but could talk after that (say 1:00?) if Arkendra is free (he is west coast time and will log in soon) –I hope to leave by 2 today since I am going out of town this eve. Are you in the office? We can both call him from here or use his call in if you are not at WO.

Kristen

From: Caposino, Paula
Sent: Friday, June 07, 2013 9:59 AM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: Beckman Troponin REsponse

Can you please review the following:
Response 1b
Response to question 13—this is the LoQ question. There is some additional information in response 2 that you may want to look at. We asked question 13 when we reviewed the response to question 2.

My question to you is, can they support a 20% CV claim at 0.02.

The line data for the LoQ study is in IMAGE (k121214) listed as Statistical data. Let me know if you need me to email this to you.

Can we chat at some point today?

Thanks,
Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD

294

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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k121214

B. Purpose for Submission:
New Device

C. Measurand:
Cardiac troponin I (cTnI)

D. Type of Test:
Quantitative paramagnetic-particle chemiluminescent immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrator for use on the Access 2 Immunoassay System

Comment [PVC1]: Double check with sponsor

G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1215 Creatine Phosphokinase/creatine kinase or isoenzymes test system
   21 CFR 862.1150 Calibrator secondary
   21 CFR 862.2160 Discrete photometric chemistry analyzer for clinical use

2. Classification:
   Class II (21 CFR 862.1215 and 21 CFR 862.1150),
   Class I (21 CFR 862.2160)

3. Product code:
   MMI, Immunoassay method, troponin subunit
   JIT, Calibrator, secondary
   JJE, Analyzer, chemistry (photometric, discrete), for clinical use

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use

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2. Indication(s) for use:
The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

3. Special conditions for use statement(s):
For prescription use, for in vitro diagnostic use, not to be used for risk stratification

Comment [PVC2]: Should this be in our DS when it is not in the labeling? It is in the Pathfast DS but not in the labeling.

Comment [RAC3]: To be the same as Pathfast we should include it here

4. Special instrument requirements:
For use on the Access 2 Immunoassay System

I. **Device Description:**
The Access AccuTnI+3 Reagent packs contain:
- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin 300
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (ng/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300. The calibrators are sold separately.

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the

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system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into the system. The APF contains all assay specific parameters used to process a particular assay.

To correct thermal sensitivity from ambient temperature fluctuations that could affect the accuracy of test results, the sponsor developed a software algorithm that normalizes troponin results. This solution was implemented through a combination of system and operating software changes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ADVIA Centaur TnI-Ultra Assay
   ADVIA Centaur TnI-Ultra Calibrators
   Access 2 Immunoassay System

2. Predicate k number(s):
   k053020 for the ADVIA Centaur TnI-Ultra Assay and ADVIA Centaur TnI-Ultra Calibrators; k922823/A007 for the Access 2 Immunoassay System

3. Comparison with predicate:

Similarities		
Item	Access AccuTnI+3 Reagent	Predicate Device (k053020)
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Primary Reagent Materials	Solid phase magnetic particles, anti cTnI antibodies	Same

Comment [c4]: To be similar to pathfast, I suggest we put this is the differences table and just state the uses (one will have risk strat and one won't). There not have the risk stratification specifically called out separately.

Differences		
Item	Access AccuTnI+3 Reagent	Predicate Device (k053020)
Risk stratification~~Indications For Use~~ use	Not for risk stratification use	For risk stratification use
Sample Types	Serum and heparinized plasma	Serum, heparinized plasma and EDTA plasma
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate,	Polyclonal goat anti-cTnI antibody labeled with

186

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Differences		
Item	Access AccuTnI+3 Reagent	Predicate Device (k053020)
	magnetic particles coated with mouse monoclonal anti-human cTnI	acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin
Acute Myocardial Infarction (AMI) Cut-Off	0.03 ng/mL validated based on clinical trial outcome	0.9 ng/mL per WHO-defined cutoff
Upper Reference Limit	99th percentile of 0.02 ng/mL	99th percentile of 0.04 ng/mL

Similarities		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Intended Use	Intended to calibrate the Access AccuTnI+3 assay.	Intended to calibrate the TnI-Ultra assay.

Differences		
Item	Access AccuTnI+3 Calibrators	Predicate Device (k053020)
Calibrator Materials	Recombinant troponin complex in buffered BSA	Bovine cTnI in goat serum
Calibrator Number And Type	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL (with no master curve)	Two lyophilized: high and low (use with Master Curve)

Similarities		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Intended Use	For the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	Same
Operating Principle	Micro computer controlled, random and continuous access	Same
Assay Type	Enzyme immunoassays	Same
Detection	Chemiluminescent	Same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems and computer/peripheral	Same

Comment [c5]: Instrument? I prefer we put the instrument and assay reagents together in this description since the instrument doesn't need clearance on its own. Only the parameters here relevant to this system need to be included.

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Differences		
Item	Access 2 Immunoassay System	Predicate Device (k922823/A007)
Thermal Algorithm Capability	Present	Not present
Assay Protocol File (APF)	AccuTnI APF with addition of the thermal algorithm and "U" command (to improve mixing of the paramagnetic particle reagent); added result suppression when instrument internal case temperature is outside 18°C to 36°C	AccuTnI APF
Software	Version 3.3	Versions 2.4-3.2
Operating Temperature	18°C to 28°C ambient	18°C to 32°C ambient

K. Standard/Guidance Document Referenced (if applicable):

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline (EP17-A2)
- Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline (EP25-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3c)

L. Test Principle:

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

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M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*
The sponsor evaluated precision in several studies based on CLSI EP5-A2.

The first 3 studies were conducted at one of 3 ambient temperature conditions. The studies performed at 18°C and 28°C were performed internally Three commercial controls, 1 recombinant cTnI-spiked lithium heparin plasma sample, and 1 pooled lithium heparin plasma sample were assayed in replicates of 2, 2 shifts per day, 2 runs per shift, for a total of 21 shifts (42 runs) over 13 days. These studies were performed on 1 instrument and 1 reagent pack lot.

Comment [PVC6]: Or 2 instruments?

The third study was performed externally under ~~normal~~ existing laboratory conditions (measured temperatures ranged from 20°C to 24°C). Six commercial controls (ranging from 0.02 ng/mL to 15 ng/mL) were run in duplicate, 2 runs per day for 20 days for a total of 40 runs. This study was performed on one reagent lot and one instrument.

The fourth study was a confirmation study that was run across multiple ambient temperatures ranging from 18°C to 28°C. The sponsor used a low spiked patient pool (sp), 3 commercial controls (c), and one high patient pool (hp). These samples were tested in duplicate in 2 runs per shift, 2 shifts per day, over 14 days. One reagent lot and on one instrument was used in this study.

The following data are representative of the results from the precision studies and are presented in the labeling:

Mean	Within-Run (%CV)	Between-Run (%CV)	Total Imprecision (%CV)
0.07 (lp)	5	5	7
0.91 (c)	2	5	5
1.96 (c)	2	5	5
13.97 (c)	2	5	5
56.36 (hp)	5	4	6

Comment [c7]: Sp? Or is the typo above?

The sponsor also determined the precision of the device using 3 low-level natural patient sample pools, 2 instrument, 2 reagent lots, multiple ambient temperatures ranging from 18°C to 28°C and multiple calibration cycles over 14 days. The samples were assayed in replicates of X in X runs per day. The results of the study are summarized below:

Mean	Total imprecision (SD, ng/mL)	Total imprecision (%CV)

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0.04	0.003	8
0.43	0.022	5
1.01	0.043	4

Field precision studies: The sponsor performed a precision studies in-house to simulate the use of the device by the end user. The first study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, reflex, stat, and individual testing); variability of ambient temperatures; and variability of instrument age. The sponsor used quality control material for the study and 3 instruments (how many reagent lots?). The sponsor cycled the temperature of the laboratory from 18 to 28 °C over the course of 6 hours over 3 days of testing. The samples were assayed in a minimum of 44 replicates on each instrument across the 3 days of testing. The results of this study are summarized below:

Instrument	Sample	Mean ng/mL	Within-instrument % CV
1	1	0.056	4.1
	2	0.641	4.6
	3	2.040	3.7
	4	0.383	5.4
	5	8.248	5.4
2	1	0.055	8.7
	2	0.636	4.9
	3	2.054	3.5
	4	0.389	6.1
	5	8.348	3.8
3	1	0.053	5.0
	2	0.594	4.6
	3	1.874	3.2
	4	0.366	4.9
	5	7.802	4.5

Comment [PVC8]: Is this true?

External Field precision study: The sponsor performed this study to evaluate the precision of the device at external sites. Commercially available quality control materials were run in duplicate (how many runs) with 3 lots of reagents on 5 instruments at 5 external sites over 10 days (sample 1 fell below the LoQ of the assay and is not listed). One instrument was used at each site. The results of these studies are summarized below:

Comment [PVC9]: If you prefer Ruth, I can put in the tables with the full data instead of the range.

Reagent lot 1

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.034 to 0.042	3.5 to 4
3	0.622 to 0.685	2.4 to 4.4

Comment [PVC10]: Is this true?

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4	0.928 to 1.04	2 to 5.2
5	2.586 to 2.813	2.5 to 4.3
6	14.19 to 16.19	1.9 to 7.4

Reagent lot 2

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.032 to 0.040	4.6 to 11
3	0.602 to 0.642	2.4 to 5.0
4	0.883 to 1.055	2.8 to 6.5
5	2.492 to 2.68	2.8 to 5.4
6	13.48 to 15.19	1.8 to 6.9

Comment [PVC11]: Is this true?

Reagent lot 3

Sample	Means (ng/mL) observed at the 5 sites	Within-lab %CVs observed at the 5 sites
2	0.030 to 0.036	4.3 to 15
3	0.0594 to 0.645	2.7 to 5.7
4	0.880 to 0.996	1.9 to 6.0
5	2.455 to 2.65	2.4 to 5.0
6	13.82 to 14.85	2.1 to 8.2

Comment [PVC12]: Is this true?

b. *Linearity/assay reportable range:*
Linearity was evaluated in accordance with the CLSI EP6-A guideline utilizing 2 reagent lots and 2 instruments at 3 different temperature conditions (from 18 to 28 °C) using lithium heparin plasma samples spiked with native cardiac troponin I analyte. The sponsor evaluated linearity using 9 pools of varying analyte concentration that spanned the reportable range of the assay. A total of x replicates at each level were analyzed with each reagent lot and instrument at each temperature (for a total of 12 independent analyses). The polynomial fit was significant for all analyses but the maximum deviation from nonlinearity was 14%. The sponsor claims acceptable linearity from 0.003 to 106.04 ng/mL.

High Dose Hook Effect: The sponsor demonstrated that there was no high dose hook effect from the concentration of the S5 calibrator (≈100 ng/mL) to 2,529 ng/mL.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access AccuTnI+3 Calibrators are standardized to an internal standard. They are identical to the previously cleared (k010429) Access AccuTnI Calibrators.

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Calibrators are value assigned using primary reference curves and verified using quality control material and patient samples that must meet specifications. The value assignment process was reviewed and found to be acceptable.

Calibrator stability: The calibrators are stable for 12 months when stored unopened at -20°C. Once opened, the calibrators are stable for 60 days when stores at 2 to 8°C. The calibrator stability protocols were reviewed and found to be acceptable.

d. *Detection limit*:
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) studies were performed following the recommendations in EP17-A2. Testing was performed over 3 days using 2 reagent packs, 3 instruments, 3 calibration cycles with 3 different temperature conditions (from 18 to 28 °C).

To estimate the LoB, 4 blank samples were measured in replicates of 10 on each day of testing on each instrument/reagent lot combination at the different temperature conditions. The LoB was established to be 0.003 ng/mL. The sponsor claims that the LoB is <0.01 ng/mL.

To estimate the LoD, 6 native lithium heparin plasma samples containing low levels of troponin I analyte were measured in 2 runs of 10 replicates each during each day of testing on each instrument/reagent lot combination at the different temperature conditions. The sponsor claims that the LoD is 0.008 ng/mL.

To estimate the LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured on each instrument/reagent lot combination at the different temperature conditions. Three instruments and 2 reagent lots were used in this study.

The sponsor claims an LoQ of 0.02 ng/mL with a performance goal of < 20% CV (within-lab). The lowest concentration with a % CV (within-lab) equal to 10% was estimated to be 0.04 ng/mL.

The sponsor provided data demonstrating that the LoQ of the device using serum samples at 3 different temperature conditions (from 18 to 28 °C) is identical to the LoQ of the device using lithium heparin plasma samples.

The sponsor claims that the reportable range of the device is 0.02 ng/mL to the S5 calibrator (approximately 100 ng/mL).

e. *Analytical specificity:*
Two levels of potential interfering substances were added to lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin at 3 different

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temperature conditions (from 18 to 28 °C). For the controls, the corresponding solvent was added to the lithium heparin plasma pools containing either 0.05 or 0.5 ng/mL troponin. Control troponin samples (control sample) and samples spiked with the potential interferents (test sample) were tested in replicates of 5 (for the 0.5 ng/mL) or X (for the 0.05 ng/mL) and compared. The sponsor used 1 reagent lot and 6 instruments for this study. The sponsor concluded that the following substances at the listed concentrations did not interfere with the performance of the device (defined as less than 10% difference between the control sample result and the test sample result).

Substance Added	Concentration	Difference observed
Acetaminophen	3 and 20 mg/dL	<10%
Acetylsalicylic Acid	50 and 65 mg/dL	<10%
Allopurinol	2 and 40 mg/dL	<10%
Ambroxol	8.6 and 40 mg/dL	<10%
Ampicillin	1.8 and 5 mg/dL	<10%
Ascorbic Acid	4 and 6 mg/dL	<10%
Atenolol	0.2 and 1 mg/dL	<10%
Bilirubin conjugated	5 and 40 mg/dL	<10%
Bilirubin unconjugated	4 and 40 mg/dL	<10%
Biotin	10 and 290 ng/mL	<10%
Caffeine	2 and 10 mg/dL	<10%
Captopril	0.5 and 5 mg/dL	<10%
Cinnarizine	4.8 and 40 mg/dL	<10%
Cocaine	1 and 2 mg/dL	<10%
Diclofenac	2 and 5 mg/dL	<10%
Digoxin	2 and 200 ng/mL	<10%
Dopamine *	30 and 65 mg/dL	<10% at 30 mg/dL, 13.8% at 65 mg/dL
Erythromycin	2 and 20 mg/dL	<10%
Fibrinogen	100 and 1000 mg/dL	<10%
Furosemide	3 and 40 mg/dL	<10%
Hemoglobin	200 and 500 mg/dL	<10%
Human Serum Albumin	5000 and 6000 mg/dL	<10%
Ibuprofen	40 and 50 mg/dL	<10%
Low MW Heparin	8 U/mL and 28.8 U/mL	<10%
Methyldopa	0.75 and 2.5 mg/dL	<10%
Nifedipine	20 and 60 µg/dL	<10%
Nitrofurantoin	0.2 and 6.4 mg/dL	<10%
Nystatin	0.7 and 2.15 mg/dL	<10%
Oxytetracycline	0.5 and 24 mg/dL	<10%
Phenytoin	5 and 10 mg/dL	<10%
Propranolol	1 and 500 µg/mL	<10%

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Quinidine	0.6 and 2 mg/dL	<10%
Simvastatin	4 and 20 μg/mL	<10%
Theophylline	2 and 25 mg/dL	<10%
Triglycerides	1000 and 3000 mg/dL	<10%
Trimethoprim	1.8 and 7.5 mg/dL	<10%
Verapamil	0.1 and 16 mg/dL	<10%
Warfarin	3 and 30 μg/mL	<10%

*For dopamine, the sponsor claims no interference up to 30 mg/dL

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma pools containing 2 levels of troponin (≤ 0.02 ng/mL and approximately 0.5 ng/mL troponin). Control and test samples were tested on 1 instrument using X reagent lots at 3 temperature conditions (from 18 to 28 °C) in replicates of X. For each possible cross-reactant tested, the troponin I concentration (ng/mL) obtained for the spiked sample was compared to the troponin I concentration obtained with the control sample and applied to the following formula: % cross reactivity = [(mean dose of spiked – mean dose of control)/amount of cross reactant spiked] X 100. The sponsor concluded that the following proteins at the concentration listed did not cross react (defined as < 1% cross reactivity) with the device.

Substance	Concentration tested ng/mL
Actin	1000
Cardiac troponin C	1000
Recombinant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

HAMA/Heterophile antibodies: The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents. They include the following in the Limitations of the Procedure section of the Instructions for Use:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

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f. Assay cut-off:
Refer to section 4 "Clinical cut-off".

2. Comparison studies:

a. Method comparison:
Not applicable.

b. Matrix comparison:
The sponsor conducted a clinical matrix comparison study to compare matched lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort. Results of Passing-Bablok regression analysis of singlicate results are provided below (the sponsor excluded 26 samples with troponin levels below the LoQ from this analysis):

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 to 20	96	1 (0.98 to 1.00)	0.00 (0 to 0)	R = 1.00
0.02 to 5				

Comment [c13]: This row will be filled in?

Clinical concordance analysis using 123 matched clinical samples from the pivotal trial cohort was performed between the 2 sample types at the 0.03 ng/mL cut-off and is provided below: The sponsor demonstrated 96% agreement between the lithium heparin plasma samples and serum samples.

	Serum < 0.03	Serum ≥ 0.03	Total
Plasma < 0.03	38	3	41
Plasma ≥ 0.03	2	80	82
Total	40	83	123

The sponsor created Receiver Operating Characteristic curves (ROC) for each matrix using result from all 123 subjects with matched serum and heparin plasma samples from the pivotal trial cohort. The areas under the ROC curve (AUC) are 0.845 and 0.847 for plasma and serum respectively.

Comment [c14]: I suggest we put this in the non-public section.

Comment [PVC15]: Let me know if we want to keep this in here or in the non public section

An additional study was performed 3 times, once at 3 different temperatures conditions (ranging from 18 to 28°C) on 2 instruments using one reagent lot. The study included 97 matched serum and lithium heparin plasma samples (not spiked or diluted) which were run at each temperature condition. Results of Passing-Bablok regression analyses of singlicate measurements are provided below:

Temp	Range (ng/mL)	Slope (95% CI)	R value	Intercept (95% CI)	n
18°C	0.02 - 77.96	1.03 (1.01 - 1.06)	0.99	-0.01 (-0.01 – 0.00)	97
23°C	0.02 - 71.76	1.02 (0.99 - 1.04)	0.99	0.00 (-0.01 – 0.00)	97
28°C	0.02 - 66.76	1.04 (1.01 - 1.06)	0.99	0.00 (-0.01 – 0.00)	97

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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3. Clinical studies:

a. *Clinical Sensitivity:*

Comment [PVC16]: Sensitivity and specificity estimates a little bit different in the labeling.

A clinical study was performed to evaluate the clinical performance of the device at the different cut-offs. A multicenter prospective study enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of presentation to the ER. The sample collection times were at baseline, 1 to 3 hours, 3 to 6 hours and 6 to 9 hours after presentation to the ER. Investigators and adjudicators were blinded to the proposed device's results. All results presented below were based on the adjudicated diagnoses. Testing was performed using lithium heparin plasma samples. The results are summarized below:

Clinical Performance at 0.03 ng/mL (this cut-off was determined in a feasibility study by ROC analysis)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	87.4 (221/253)	83.3-91.4	89.3 (1495/1675)	87.8-90.7
1-3 h	96.0 (119/124)	92.5-99.4	89.4 (907/1014)	87.6-91.3
3-6 h	94.9 (149/157)	91.5-98.3	86.7 (816/941)	84.5-88.9
6-9 h	90.7 (39/43)	82.0-99.4	87.0 (214/246)	82.8-91.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	55.1 (221/401)	50.2-60.0	97.9 (1495/1527)	97.2 to 98.6
1-3 h	52.6 (119/226)	46.1-59.2	99.5 (907/912)	99.0-99.9
3-6 h	54.4 (149/274)	48.5-60.3	99.0 (816/824)	98.4-99.7
6-9 h	54.9 (39/71)	43.4-66.5	98.2 (214/218)	96.4-99.9

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	91.5 (151/165)	87.3-95.8	89.1 (885/993)	87.2-91.1
≥ 8 h	94.3 (150/159)	90.7-97.9	86.8 (966/1113)	84.8-88.8

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	58.3 (151/259)	52.3-64.3	98.4 (885/899)	97.6-99.3
≥ 8 h	50.5 (150/297)	44.8-56.2	99.1 (966/975)	98.5-99.7

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Clinical Performance at 0.02 ng/mL (99th percentile upper reference limit)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	92.1 (233/253)	88.8-95.4	84.3 (1412/1675)	82.6-86.0
1-3 h	98.4 (122/124)	96.2-100	85.5 (867/1014)	83.3-87.7
3-6 h	98.1 (154/157)	95.9-100	81.0 (762/941)	78.5-83.5
6-9 h	93.0 (40/43)	85.4-100	76.4 (188/246)	71.1-81.7

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	47.0 (233/496)	42.6-51.4	98.6 (1412/1432)	98.0-99.2
1-3 h	45.4 (122/269)	39.4-51.3	99.8 (867/869)	99.5-100
3-6 h	46.2 (154/333)	40.9-51.6	99.6 (762/765)	99.2-100
6-9 h	40.8 (40/98)	31.1-50.5	98.4 (188/191)	96.7-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	96.4 (159/165)	93.5-99.2	83.2 (826/993)	80.9-85.5
≥ 8 h	96.9 (154/159)	94.1-99.6	81.7 (909/1113)	79.4-83.9

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	48.8 (159/326)	43.3-54.2	99.3 (826/832)	98.7-99.9
≥ 8 h	43.0 (154/358)	37.9-48.1	99.5 (909/914)	99.5-99.9

Clinical Performance at 0.04 ng/mL (lowest measured concentration with a %CV (within-lab) of <10%)

Based on sample collection timepoint:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
Baseline	77.1 (195/253)	71.9-82.3	93.9 (1572/1675)	92.7-95.0
1-3 h	89.5 (111/124)	84.1-94.9	93.5 (948/1014)	92.0-95.0
3-6 h	87.3 (137/157)	82.0-92.5	93.0 (875/941)	91.4-94.6
6-9 h	90.7 (39/43)	82.0-99.4	93.1 (229/246)	89.9-96.3

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
Baseline	65.4 (195/298)	60.0-70.8	96.4 (1572/1630)	95.5-97.3
1-3 h	62.7 (111/177)	55.6-69.8	98.6 (948/961)	97.9-99.4
3-6 h	67.5 (137/203)	61.0-73.9	97.8 (875/895)	96.8-98.7

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6-9 h	69.6 (39/56)	57.6-81.7	98.3 (229/233)	96.6-100

Based on hours since symptom onset:

Interval	Sensitivity		Specificity	
	%	95% CI	%	95% CI
< 8 h	85.5 (141/165)	80.1-90.8	93.6 (929/993)	92.0-95.1
≥ 8 h	88.1 (140/159)	83.0-93.1	92.7 (1032/1113)	91.2-94.2

Interval	Positive Predictive Value		Negative Predictive Value	
	%	95% CI	%	95% CI
< 8 h	68.8 (141/205)	62.4-75.1	97.5 (929/953)	96.5-98.5
≥ 8 h	63.3 (140/221)	57.0-69.7	98.2 (1032/1051)	97.4-99.0

b. *Clinical specificity:*
See clinical specificity information above in 3a.

c. *Other clinical supportive data (when a. and b. are not applicable):*

4. Clinical cut-off:
This assay has 2 claimed clinical cut-offs. One cutoff (0.03) was determined in a feasibility study by ROC analysis. The second cut-off (0.02) is the 99th percentile upper reference limit. The sponsor also provided clinical performance information in the package insert at 0.04 ng/mL which is the lowest concentration with a %CV (within-lab) of <10%.

5. Expected values/Reference range:
The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. 527 subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included reference range study to determine the 99th percentile upper reference limit.

The 99th percentile upper reference limit was demonstrated to be 0.02 ng/mL (95% CI: 0.01 to 0.05).

N. Instrument Name:
Access 2 Immunoassay System

O. Systems Descriptions:
1. Modes of Operation:
Micro computer controlled analyzer with random and continuous access.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

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Yes __X___ or No ____

Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
Yes _____ or No __X__

2. Software:
   FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
   Yes __X___ or No _____

3. Specimen Identification:
   Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
   Instruction on sample handling is provided in the reagent labeling.

5. Calibration:
   An active calibration curve is required for all tests. For the Access AccuTnI assay, calibration is required every 56 days.

6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Ambient temperature method comparison studies: The sponsor provided data from 4 studies (3 studies focused on low dose (LD) troponin concentrations around the cut-offs (0.02 – 0.4. ng/mL) and 1 study evaluating the full reportable range (FR) of the assay) to demonstrate the impact of ambient temperature differences on the test result. Seven hundred fifty one (751) lithium heparin plasma samples were tested in total at different temperature conditions (ranging from 18 to 28°C) on multiple instruments using multiple reagent lots. Samples were divided into aliquots, and tested at different temperatures. The sponsor analyzed the same samples run under different temperature conditions using Passing-Bablok analysis of singlicate test results: The results of 19 different comparisons provided by the sponsor from the 4 different studies are summarized below:

Comment [PVC17]: Check pre-verifcation is this low dose or full range, check additional concorande studies are these low dose or full range.

Study	Low temp	High temp	n	Slope (95% CI)	Intercept (95% CI)	r^2
1	18°C	26°C	57	1.04 (1.00, 1.08)	0.01 (0.00, 0.01)	0.97
	18°C	22°C	59	1.00 (0.97, 1.02)	0.00 (0.00, 0.00)	0.99

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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	22°C	26°C	57	1.05 (1.02, 1.08)	0.00 (0.00, 0.01)	0.98
	20°C	28°C	61	0.97 (0.92, 1.03)	0.00 (0.00, 0.01)	0.96
	20°C	24°C	61	0.98 (0.95, 1.01)	0.00 (0.00, 0.00)	0.99
	24°C	28°C	61	1.00 (0.95, 1.04)	0.00 (0.00, 0.01)	0.98
2 LD	18°C	26°C	76	0.93 (0.90, 0.97)	0.00 (0.00, 0.01)	0.97
	18°C	22°C	75	0.99 (0.97, 1.01)	0.00 (0.00, 0.00)	0.99
	22°C	26°C	75	0.94 (0.91, 0.97)	0.01 (0.00, 0.01)	0.99
	20°C	28°C	78	0.95 (0.90, 0.98)	0.01 (0.00, 0.01)	0.99
	20°C	24°C	78	0.99 (0.96, 1.01)	0.00 (0.00, 0.01)	0.99
	24°C	28°C	78	0.96 (0.93, 0.99)	0.00 (0.00, 0.00)	0.99
3 LD	18°C	28°C	379	0.94 (0.93, 0.95)	0.00 (0.00, 0.00)	0.99
4 LD	18°C	28°C	42	1.00 (0.96, 1.05)	0.00 (0.00, 0.00)	0.99
	18°C	23°C	42	0.98 (0.94, 1.02)	0.00 (0.00, 0.01)	0.99
	23°C	28°C	42	1.03 (1.00, 1.06)	0.00 (0.00, 0.00)	0.99
4 FR	18°C	28°C	102	0.98 (0.97, 0.99)	0.00 (0.00, 0.00)	1.00
	18°C	23°C	102	1.02 (1.00, 1.03)	0.00 (-0.01, 0.00)	1.00
	23°C	28°C	102	0.96 (0.95, 0.98)	0.01 (0.00, 0.01)	0.99

Q. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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S. Other Supportive Device and Instrument Information:

Additional Linearity data: The sponsor also evaluated the linearity of the lower end of the measuring range (using lithium heparin samples) by performing a study with samples from 0.006 to 1.5 ng/mL (0.006, 0.15, 0.30, 0.60, 0.90, 1,17, 1.50 ng/mL) at different temperatures. For 18 and 23°C, the polynomial fit was not significant. For the 28°C, the polynomial fit was significant but the maximum deviation from nonlinearity was 1%.

T. Administrative Information:

1. *Applicant contact information:*

a. Name of applicant:	Beckman Coulter Inc.
b. Mailing address:	1000 Lake Hazeltine Drive Chaska, MN 55318
c. Phone #:	(952)368-7858
d. Fax #:	(952)368-7610
e. E-mail address (optional):	ksoetter@beckman.com
f. Contact:	Kerrie S. Oetter

2. Review documentation:

3. Substantial Equivalence Discussion:

	Yes	No	
1. Same Indication Statement?	X		If YES = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NSE
3. Same Technological Characteristics?	X		If YES = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If NO = Go To 8 If YES = Stop SE
6. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NSE
7. Accepted Scientific Methods Exist?			If NO = Stop NSE
8. Performance Data Available?	X		If NO = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: CS

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for

201

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Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

a. *Explain how the new indication differs from the predicate device's indication:*

b. *Explain why there is or is not a new effect or safety or effectiveness issue:*

c. *Describe the new technological characteristics:*

d. *Explain how new characteristics could or could not affect safety or effectiveness:*

e. *Explain how descriptive characteristics are not precise enough:*
Because the clinical use of this *in vitro* diagnostic device is based upon its performance characteristics, descriptive characteristics alone are not sufficient to support a claim of substantial equivalence to legally marketed in vitro diagnostic devices.

f. *Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:*

g. *Explain why existing scientific methods can not be used:*

h. *Explain what performance data is needed:*
See section M of the SE review template.

i. *Explain how the performance data demonstrates that the device is or is not substantially equivalent:* The submitted information in this premarket notification is complete and supports a substantial equivalence decision. See the decision summary template section M – performance characteristics above for more information.

U. Reviewer Name and Signature:

Paula Caposino, Ph.D.
CDRH/OIVD/DCTD

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Chesler, Ruth A
Sent: Thursday, June 13, 2013 8:59 AM
To: Pilcher, Ian; Caposino, Paula; Lias, Courtney H
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

I agree with Ian that each event could have multiple erroneous results, therefore I think 20- 25 would be a much better number than 100. Also I am wondering about the timeline for reporting these events to FDA if they use their standard risk evaluation and management processes – would it be the same as for MDR (which is pretty long)?

Ruth

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 8:44 AM
To: Caposino, Paula; Lias, Courtney H; Chesler, Ruth A
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

They have not proposed any additional monitoring beyond their typical complaint system and their rapid response team.

From: Caposino, Paula
Sent: Thursday, June 13, 2013 8:38 AM
To: Lias, Courtney H; Pilcher, Ian; Chesler, Ruth A
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

I worry about agreeing with the upper limit of 100 as well. I think it is good that FDA will be informed at the 5 threshold.
Would we consider having them lower the threshold to 20ish but change the corrective action to:
All of the above plus…
Stop ship product (with FDA agreement)
Cease use notification to customers (with FDA agreement)
That way we can discuss at that time if that is a reasonable corrective action.

Have they proposed monitoring? I don't believe that they have unless we consider this rapid response team as monitoring.

Thanks.
Paula

From: Lias, Courtney H
Sent: Thursday, June 13, 2013 8:21 AM
To: Pilcher, Ian; Caposino, Paula; Chesler, Ruth A
Subject: RE: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Thanks Ian.

We typically do not ask for postmarket agreements for premarket decisions, but this case is special. This 510(k)k is the result of 2 major recalls, and they are instituting a fix that is validated with conflicting data. If they want us to feel like we can make a decision that this device will; be as safe and effective as predicate devices, we need to be assured that some mitigation is in place to address this potential test performance issue. In this case, that mitigation is increased monitoring and a plan for addressing this anticipated problem should it arise. In our response this morning, please let BC know this.

203

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

I agree that 100 is too high. They should begin an investigation if they even see 1 event. I was assuming their threshold for more action was 5 events based on what you said they proposed at first. However, I think something between 5 and 100 is reasonable as well. I wouljd think if they see 20 events (with an "event' being one reported, or one set of reported, incidents confirmed by BC as having been caused by thermally insensitive samples). What does the rest of this group think?

From: Pilcher, Ian
Sent: Thursday, June 13, 2013 8:11 AM
To: Caposino, Paula; Chesler, Ruth A; Lias, Courtney H
Subject: FW: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Beckman's response to our question about how they will proceed if they determine that labs are encountering thermally insensitive samples is below. They have added a third step in which they would stop shipping the product and notify users to stop using it with FDA's agreement. Their threshold for the third option is 100 discrete events per year. This seems like a high number and I would expect them to take this type of action at a much lower threshold, especially since each of these discrete events could contain numerous erroneous results. In the body of the e-mail itself they also state that they are unaware of of any other case where we have required a firm to agree in advance to withdraw a product from the market without going through their normal processes. They also believe that this is not authorized by statute or resolution and that it does not add anything to public health and they ask us to reconsider if such a step is appropriate. They do not include any information on how they will proceed or the steps they will take to remove their current device from the market if their current submission does not show their device to be SE. I don't think we have asked them for this recently, is this something we should be doing considering the timelines and issues with this device?

Please let me know your thoughts on this and how we should respond to this e-mail.

thanks,

an

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity

Hello Ian,

Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a

204

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precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

incerely,
ɔcott Cundy

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205

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Caposino, Paula

rom: Cundy, Scott T <STCundy@beckman.com>
ent: Thursday, June 13, 2013 12:08 AM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC"s Response to June 10, 2013 Additional Information - Thermal Insensitivity
Attachments: Response to e-mail questions June 10 A2 AI Request (6-12-13) Final.pdf

Hello Ian,

Attached is BEC's response to FDA's June 10 request for additional information. The response indicates how we would respond to reports of thermal insensitivity, including possible withdrawal. In the interest of resolving the issues the agency continues to have regarding the anomalous results in the original submission, we have put in the language you requested indicating the circumstances in which withdrawal of the product from the market is a possible outcome. However, we are advised that being required to agree in advance to withdraw a product from the market without going through the normal processes in cases in which such an outcome might be on the table is not only unknown in any advisors' previous experience, but that such a condition regarding post-market occurrences is not authorized by statute or regulation. We do not think that establishing pre-defined criteria adds anything to public health given that under our standard risk evaluation and management processes, we would act appropriately, including withdrawing a product if that action was warranted. Accordingly, we would ask that you reconsider whether establishing pre-defined numerical thresholds is appropriate here. In any event, FDA should not deem the attached response as setting a precedent for any future submission or our agreeing that establishing post-market conditions of this sort is consistent with the law.

Sincerely,
Scott Cundy

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Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Thermal

FDA: After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

BEC Response to Question 1

BEC has established an AccuTnI+3 Early Response Team (ERT), to closely monitor the performance of AccuTnI+3 assay for the Access2 instrument for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the AccuTnI+3 assay commercialization for the Access2 instrument, including product performance.

The AccuTnI+3 ERT facilitates real-time cross-functional surveillance of all customer feedback related to the AccuTnI+3 assay. ERT surveillance accelerates investigation into potential product performance issues during the early phase of AccuTnI+3's product release, allowing us to evaluate potential issues before reaching our traditional product escalation thresholds. Therefore, a single report of a potential product performance failure, regardless of the severity and magnitude of the failure, will be rapidly addressed by the ERT. The ERT will investigate all reports of potential "thermal insensitivity" as well as any other unexpected product performance failures.

If thermally insensitive samples are identified and confirmed on the Access2 instrument, BEC will use a risk management approach to determine the appropriate corrective action. For AccuTnI+3 assay, the probability of thermally insensitive samples causing falsely increased or decreased results, resulting in a potentially hazardous situation, has been determined to be Remote according to BEC's risk management process. Since we do not have any historical occurrence rates for this new failure mode, we will use discrete events for determination of the trigger threshold versus an occurrence rate. BEC believes that selecting a specific number of discrete events to trigger action is more conservative than selecting an occurrence rate given the lack of historical information and the large number of tests sold per year (> 28 million). BEC defines the occurrence of 1-4 annual discrete events for the potentially hazardous situation as a Remote occurrence.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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If US annual discrete events on the Access2 instrument = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s) (see **Table 1-1** below)
4. Continue post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

If US annual discrete events on the Access2 instrument ≥ 100 (Very high incidence rate)

1. Stop ship product
2. Cease use notification to customers (with FDA agreement)

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased clinically relevant result(s) where the increase or decrease is proven to be caused by inappropriate adjustment by the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

The actual corrective action(s) depend on the frequency, magnitude, severity, and root cause. Several potential outcomes are possible, and would be driven by the risk assessment and CAPA. Examples of potential corrective actions are identified in **Table 1-1** below:

Table 1-1: Potential Corrective Actions in Event of Failure on the Access2 Instrument

Frequency	Potential Corrective Action
Low incidence (1-4 US annual discrete events)	Customer communication and/or Labeling Change • Technical Bulletin • Important Product Notification • Labeling change (updates to IFU) • Design Change
High incidence ($5 \leq n \leq 99$ US annual discrete events)	All of the above plus… Product CAPA Product Corrective Action escalation Communication to FDA
Very High incidence (≥ 100 US annual discrete events)	All of the above plus… Stop ship product Cease use notification to customers (with FDA agreement)

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The AccuTnI+3 ERT process will rapidly identify and address any product performance issues experienced by customers, including thermally insensitive samples should they occur. This process is directed by and staffed with subject matter experts who have been intimately involved in the development of the thermal algorithm and the AccuTnI+3 reagents, and customer support of the current troponin assay. BEC is committed to this plan to ensure that appropriate action is taken in the event of any AccuTnI+3 performance failure on the Access2 instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Wednesday, June 12, 2013 7:23 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: AccuTnI+3 Access 2 IFU word version (2).docx

Dear Paula,

We will send you the documents you requested tomorrow.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 5:46 PM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: AccuTnI+3 Access 2 IFU word version (2).docx
Importance: High

Dear Kerrie,
Please see my suggested edits to your IFU. Let me know if you have any questions or if you would like to discuss these suggested edits.
Thanks,
Paula

I will need the 510(k) Summary, Indications for use form, the responses to the questions that I sent you and the IFU tomorrow. I am very sorry that I cannot give you more time.

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210

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AccuTnI+3

REF A98143 **FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2**

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy."[12]

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Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV make determination of a significant change more difficult but do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos® 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)

Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin™ 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi, Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

Comment [PVC1]: Please include a statement that patient samples cannot be diluted because this could lead to lower than expected troponin test results. Or something similar.

1. For use on sSerum and lithium heparin plasma ~~are preferred~~ samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]

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- Follow blood collection tube manufacturer's recommendations for centrifugation.
- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty-five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good

Comment [PVC2]: We recommend that you include a recommendation that the user should use commercially available samples near the cut-off. You should consider giving an example (i.e., MORE) or add a statement that the user should call customer service for advice on QC samples to use.

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laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. ~~All or optimal performance,~~ ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). ~~The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]~~

~~Access AccuTnI+3 Result (X) on Access 2~~	~~Report result (X) as:~~
~~X < 0.01 ng/mL (LoD)~~	~~Troponin I not detected; result < 0.01 ng/mL~~
~~0.01 ng/mL (LoD) ≤ X < 0.02 ng/mL (20% CV LoQ)~~	~~X ng/mL, interpret result with caution due to higher assay imprecision~~
~~X ≥ 0.02 ng/mL (20% CV LoQ)~~	~~X ng/mL~~
~~X > ~100 ng/mL (S5 calibrator value)~~	~~> ~100 ng/mL~~

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.

Comment [PVC3]: Please include a limitation that patient samples cannot be diluted because this could result in lower than expected troponin test results. Or something similar.

Comment [PVC4]: Please remove this recommendation. The lower reportable range of troponin should be defined by the LoQ. The reason is that we do not know what the clinical impact may be of reporting troponin values with such high imprecision.

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7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

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Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

Comment [PVC5]: Can you also include that the adjudicators were blinded to the site diagnoses?

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Comment [PVC6]: For your sensitivity, specificity, positive predictive value and negative predictive value, please add how you arrived at your estimate (i.e., 87.4 (221/253)).

Comment [PVC7]: 1.Please make sure that your estimates (and the associated 95% CI) are consistent with the data provided in response to question 3d in the December 14th response (i.e., 95% CI calculated using the Exact Method). There seems to be a mistake in the ≥ 3 to 6 hours for the 0.03 cut-off. While the submission lists the 95% CI as 90.2-97.8, the package insert lists it as 90 to 99. Please correct any discrepancies in the package insert.

Comment [PVC8]: Please include the clinical performance of your device at 0.04 ng/mL and indicate that 0.04 ng/mL is the lowest measured concentration with a %CV (within-lab) <10%. Or something similar. Please make sure to address comments 6 and 7 above. Please include sensitivity, specificity, positive predictive value and negative predictive value.

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94– 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Comment [PVC9]: Please see comments 6, 7 and 8 above.

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

Comment [PVC10]: Please include your definition of no interference (e.g., defined as less than 10% difference between the control sample result and the test sample result).

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Substance	Highest Concentration Added	Substance	Highest Concentration Added
Acetaminophen	20 mg/dL	Furosemide	40 mg/dL
Acetylsalicylic Acid	65 mg/dL	Hemoglobin	5 mg/mL
Allopurinol	40 mg/dL	Human Serum Albumin	6000 mg/dL
Ambroxol	40 mg/dL	Ibuprofen	50 mg/dL
Ampicillin	5 mg/dL	Low MW Heparin	28.8 U/mL
Ascorbic Acid	6 mg/dL	Methyldopa	2.5 mg/dL
Atenolol	1 mg/dL	Nifedipine	60 µg/mL
Bilirubin (conjugated)	40 mg/dL	Nitrofurantoin	6.4 mg/dL
Bilirubin (unconjugated)	40 mg/dL	Nystatin	2.15 mg/dL
Biotin	290 ng/mL	Oxytetracycline	24 mg/dL
Caffeine	10 mg/dL	Phenytoin	10 mg/dL
Captopril	5 mg/dL	Propranolol	500 µg/mL
Cinnarizine	40 mg/dL	Quinidine	2 mg/dL
Cocaine	2 mg/dL	Simvastatin	20 µg/mL
Diclofenac	5 mg/dL	Theophylline	25 mg/dL
Digoxin	200 ng/mL	Triglycerides	3000 mg/dL
Dopamine	30 mg/dL	Trimethoprim	7.5 mg/dL
Erythromycin	20 mg/dL	Verapamil	16 mg/dL
Fibrinogen	1000 mg/dL	Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

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Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

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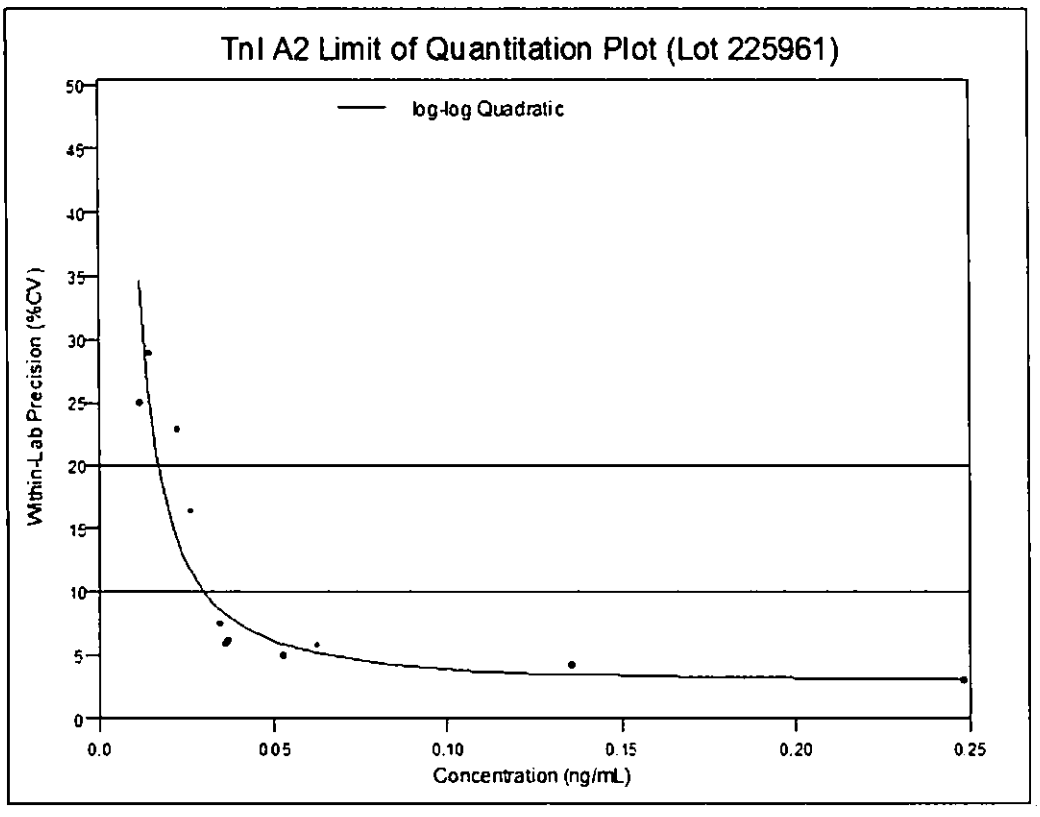

Comment [PVC11]: We recommend that you remove this graph. If you want to include a representative limit of quantitation plot, we recommend that you include the graph "Run temp 28 degrees" (Figure 13-5) from the June 4th response under "Third AI letter". The reason for this is that the performance at 28 degrees is more representative of the overall imprecision of your device.

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223

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Wednesday, June 12, 2013 6:01 PM
To: Caposino, Paula; Kerrie Oetter (koetter@live.com)
Cc: Cundy, Scott T
Subject: RE: k121214 suggested edits to Intended Use Statement

Dear Paula,

I will implement the suggested edits.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 4:52 PM
To: Kerrie Oetter (koetter@live.com); Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: k121214 suggested edits to Intended Use Statement

Dear Kerrie,
Please find enclosed my suggested edits to the Indication for Use Form:

Device name: Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrator for use on the Access 2 Immunoassay System

Indications for Use:

The Access AccuTnI+3 Reagent is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 Reagent for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Please make the following changes: Concurrence of CDRH, Office of In Vitro ~~Devices~~ Diagnostics and Radiological Health (OIR)
Division Sign-Off
Office of In Vitro ~~Devices~~ Diagnostics and Radiological Health ~~Evaluation and Safety~~

Thanks,
Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer

224

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
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Caposino, Paula

From: De, Arkendra
Sent: Wednesday, June 12, 2013 5:29 PM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Revised Text

I think that their method of analysis underestimates the variability since they are averaging.
This might be why their standard deviation results are lower than FDA's results.
I recommend the following be sent to the sponsor, in which they revise their calculations for the precision study.

To the sponsor:
1. You state in your revision to the answer to question 1 that you used an ANOVA model with only run as an independent variable for each temperature-instrument combination.
Results were averaged for each instrument-temperature combination to yield the within-lab standard deviation. Averaging results in this manner could underestimate the variability in results, as depicted in your response dated June 10, 2013 to question 2. We recommend that you report and calculate the within-lab standard deviation by computing the standard deviation for all results combined across all temperature-instrument combinations, separately for each sample, so that the variability is not underestimated. Below are FDA's results using this recommendation.

Sample ID	Mean	Within-Lab Standard Deviation	%CV
1	0.011	0.0042	38.181818
2	0.014	0.0051	36.428571
3	0.023	0.0059	25.652174
4	0.026	0.0054	20.769231
5	0.037	0.0032	8.648649
6	0.038	0.0034	8.947368
7	0.053	0.0036	6.792453
8	0.063	0.0052	8.253968
9	0.138	0.0081	5.869565
10	0.254	0.0144	5.669291
11	0.036	0.0036	10.000000

From: Caposino, Paula
Sent: Wednesday, June 12, 2013 1:46 PM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: FW: Revised Text

FYI, they updated the response to this question. Does this change anything?

Note to File: This was not communicated to the sponsor. Arkendra analysed the data and we realized that the sponsor's estimates are O.K. See Arkendra's June 13th, 2013 email.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOIASTATUS@fda.hhs.gov or 301-796-8118

226

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Wednesday, June 12, 2013 3:55 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Beckman Coulter response to k121214 June 7 AI Request
Attachments: k121214 Access AccuTnI+3 Access 2 Labels.pdf; 510(k) Summary AccuTnI+3 Access 2.doc; AccuTnI+3 Access 2 IFU word version.docx

Importance: High

Dear Paula,

I have attached the word version of our 510(k) Summary and IFU (please note that the word version of IFU will be look different – formatting and graphics have changed some when it was transferred from an Adobe FrameMaker to word version). I have also attached the PDF version of our labels. We are unable to changes our labels to word files. Please just annotate any changes on the PDF copy.

The trade names used for the product are Access AccuTnI+3 Reagent , Access AccuTnI+3 Calibrators and Access 2 Immunoassay System. The product name is the Access AccuTnI+3 Assay. It is a little complicated, these three individual items do not function on their own, but together with a patient sample, wash buffer and substrate, the Assay as a whole is culminated. With this culmination, ability to deliver the patient result is achieved, which is ultimately the goal. There are times when it is necessary to refer to the Assay as a whole, and times when it is important to refer to the components individually. We cannot always use Access AccuTnI+3 Reagents or Access AccuTnI+3 Assay exclusively, as they do mean different things.

Let me know if you have any questions.

Thanks,
Kerrie

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 10:29 AM
To: Oetter, Kerrie S
Cc: Cundy, Scott T
Subject: RE: Beckman Coulter response to k121214 June 7 AI Request
Importance: High

Good morning:
I will need some help today getting some clarification and additional details. To get this started, can you please clarify if your trade name is Access AccuTnI+3 Reagent or the Access AccuTnI+3 Assay. We recommend that you change wherever you list the device as Access AccuTnI+3 Assay to Access AccuTnI+3 Reagent (i.e., (510(k) Summary and IFU))or vice versa. We just need this to be consistent. If you could send me a word version of your IFU and your 510(k) Summary, I can send you back a list of the changes we recommend to these documents.
Also, would send me a word version of your labeling? We have some changes we would like to recommend and I think it may be best to have it as a Word File.

227

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Let me know if you agree.
Thanks,
Paula

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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is k121214

Submitted By:

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1142
Fax: (952) 368-7610

Contact Person:

Kerrie Oetter
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-7858
Fax: (952) 368-7610

Date Prepared:

June 12, 2013

Device Name:

Proprietary / Trade Name: Access AccuTnI+3 Reagent and Calibrator for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215
Classification Product Code: MMI
Subsequent Product Code: JIT

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160
Classification Product Code: JJE

Predicate Devices:

The Access AccuTnI+3 reagent and calibrators claim substantial equivalence to the TnI-Ultra™ Assay and Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Device Description:

The Access AccuTnI+3 reagents, AccuTnI+3 calibrators and the Access 2 Immunoassay System compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI+3 reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

Intended Use:

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI+3 reagent and calibrators and the predicate device, ADVIA Centaur® TnI-Ultra™ reagent and calibrators, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Similarities between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Calibrators
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same

Differences between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Calibrators
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2 Immunoassay System
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized: high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.02 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.9 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.042 ng/mL	Total CV of ≤8% at concentrations >0.075 ng/mL. SD ≤0.006 at concentrations ≤0.075 ng/mL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3 Reagent and Calibrators
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction. The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 System K922823/A007	New Device Access 2 System
Indication for Use	The Access 2 Immunoassay system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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AccuTnI+3

REF A98143 **FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2**

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy."[12]

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)

Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

   Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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- Samples may be stored for six months at -20°C.

3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access 2
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's

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instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]

Access AccuTnI+3 Result (X) on Access 2	Report result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result < 0.01 ng/mL
0.01 ng/mL (LoD) ≤ X < 0.02 ng/mL (20% CV LoQ)	X ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% CV LoQ)	X ng/mL
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.

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8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate

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sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11*] Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94– 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

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Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

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PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

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Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added	Substance	Highest Concentration Added
Acetaminophen	20 mg/dL	Furosemide	40 mg/dL
Acetylsalicylic Acid	65 mg/dL	Hemoglobin	5 mg/mL
Allopurinol	40 mg/dL	Human Serum Albumin	6000 mg/dL
Ambroxol	40 mg/dL	Ibuprofen	50 mg/dL
Ampicillin	5 mg/dL	Low MW Heparin	28.8 U/mL
Ascorbic Acid	6 mg/dL	Methyldopa	2.5 mg/dL
Atenolol	1 mg/dL	Nifedipine	60 µg/mL
Bilirubin (conjugated)	40 mg/dL	Nitrofurantoin	6.4 mg/dL
Bilirubin (unconjugated)	40 mg/dL	Nystatin	2.15 mg/dL
Biotin	290 ng/mL	Oxytetracycline	24 mg/dL
Caffeine	10 mg/dL	Phenytoin	10 mg/dL
Captopril	5 mg/dL	Propranolol	500 µg/mL
Cinnarizine	40 mg/dL	Quinidine	2 mg/dL
Cocaine	2 mg/dL	Simvastatin	20 µg/mL
Diclofenac	5 mg/dL	Theophylline	25 mg/dL
Digoxin	200 ng/mL	Triglycerides	3000 mg/dL
Dopamine	30 mg/dL	Trimethoprim	7.5 mg/dL
Erythromycin	20 mg/dL	Verapamil	16 mg/dL
Fibrinogen	1000 mg/dL	Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.

Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

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Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.

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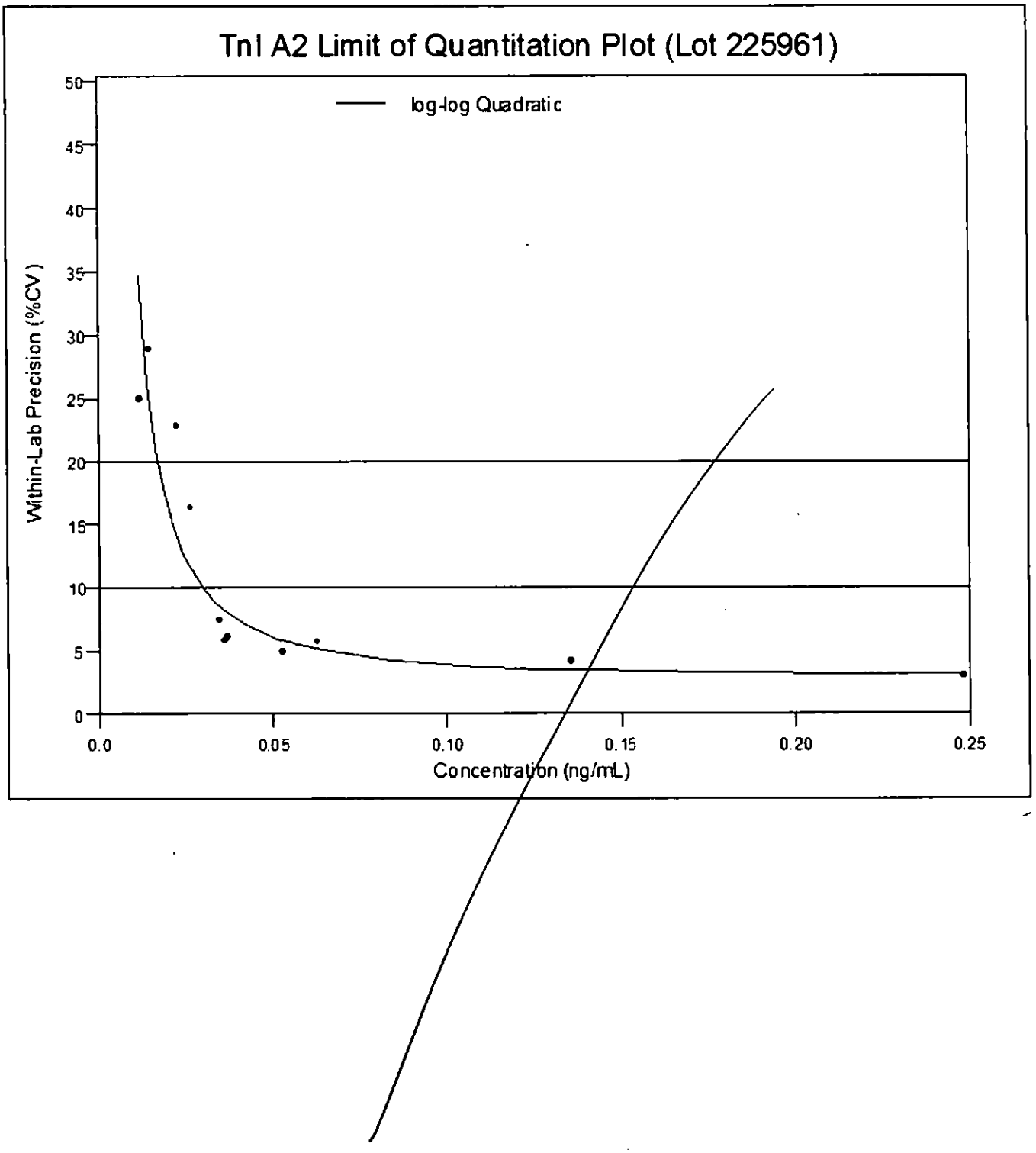

246

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AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)

Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

247

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

248

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249

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250

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Wednesday, June 12, 2013 1:19 PM
To: Caposino, Paula
Subject: RE: Revised Text

Great.

Thanks.

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 12:19 PM
To: Cundy, Scott T
Subject: RE: Revised Text

Dear Scott,
No need. I can add this to the file.
Thanks
Paula

From: Cundy, Scott T [mailto:STCundy@beckman.com]
Sent: Wednesday, June 12, 2013 1:17 PM
To: Caposino, Paula
Subject: Revised Text

Hello Paula,

Yesterday we sent you a response to your LoQ question. I need to revise the text slightly. Sorry for the confusion. The data does not change and the results do not change. The description of our analysis changes slightly. I have attached our revised text and will plan to submit it to the DMC.

Thank you,
Scott

1. **Limit of quantitation (LoQ)**

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

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Caposino, Paula

From: Cundy, Scott T <STCundy@beckman.com>
Sent: Wednesday, June 12, 2013 1:17 PM
To: Caposino, Paula
Subject: Revised Text
Attachments: Response to June 7- Q1 revision.docx

Hello Paula,

Yesterday we sent you a response to your LoQ question. I need to revise the text slightly. Sorry for the confusion. The data does not change and the results do not change. The description of our analysis changes slightly. I have attached our revised text and will plan to submit it to the DMC.

Thank you,
Scott

1. **Limit of quantitation (LoQ)**

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

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BECKMAN COULTER.

Responses to FDA's June 7, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Limit of quantitation (LoQ)

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

BEC Response to Question 1

Within each run temperature, three instruments were each calibrated at three different temperatures, providing nine testing scenarios. The three days and two runs per day for each testing scenario were seen as six runs with 10 replicates for each run (60 total replicates). A simple analysis of variance (ANOVA) with troponin in ng/mL as the dependent variable and run as the independent variable was performed using a generalized linear model (EP15-A2) to provide within-run and between-run standard deviations with their combination being within-laboratory standard deviations (SD).

For each sample, the within-laboratory variances and mean values from all nine scenarios were averaged. The coefficient of variation (CV) was computed for each sample by first taking the square root of its within-laboratory variance to obtain standard deviation and then dividing by the average mean value. The resultant precision profile analysis using the mean and %CV for each sample provided an estimate of 10% LoQ at 0.04 ng/mL and 20% LoQ at 0.02 ng/mL for troponin in the same manner as Appendix D in CLSI EP17-A2.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

rom: Cundy, Scott T <STCundy@beckman.com>
ent: Wednesday, June 12, 2013 12:10 PM
To: Pilcher, Ian; Caposino, Paula
Cc: Oetter, Kerrie S
Subject: BEC's Proposed Action Plan in the Event of a Thermally Insensitive Sample
Attachments: K121214 response to e-mail questions June 10 A2 AI Request.pdf

Hello Ian,

Attached is BEC's proposed action plan in the event that we encounter a thermally insensitive sample. The report is due to the FDA today by 2 PM EST. I'm wondering if you might be open to reviewing the document, and then giving me a quick call to discuss. I want to be sure that we are satisfying the agency's request. I thought it might be useful if we talked before it is due so that if I need to add something, I would still have time.

Please let me know your thoughts.

Thank you so much,
Scott

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Responses to FDA's June 10, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Thermal

FDA: After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

BEC Response to Question 1

BEC has established an AccuTnI+3 Early Response Team (ERT), to closely monitor the performance of AccuTnI+3 for the first 12 months after commercialization. This is a multi-functional team of troponin subject matter experts, including representatives from development, manufacturing, quality, customer and technical support, complaint handling, product management, regulatory, and program management. It is the responsibility of this team to review customer complaints, and rapidly address any issue related to the AccuTnI+3 assay commercialization, including product performance.

The AccuTnI+3 ERT facilitates real-time cross-functional surveillance of all customer feedback related to the AccuTnI+3 assay. ERT surveillance accelerates investigation into potential product performance issues during the early phase of AccuTnI+3's product release, allowing us to evaluate potential issues before reaching our traditional product escalation thresholds. Therefore, a single report of a potential product performance failure, regardless of the severity and magnitude of the failure, will be rapidly addressed by the ERT. The ERT will investigate all reports of potential "thermal insensitivity" as well as any other unexpected product performance failures.

If thermally insensitive samples are identified and confirmed, BEC will use a risk management approach to determine the appropriate corrective action. For AccuTnI+3, the probability of thermally insensitive samples causing falsely increased or decreased results, resulting in a potentially hazardous situation, has been determined to be Remote according to BEC's risk management process. Since we do not have any historical occurrence rates for this new failure mode, we will use discrete events for determination of the trigger threshold versus an occurrence rate. BEC believes that selecting a specific number of discrete events to trigger action is more conservative than selecting an occurrence rate given the lack of historical information and the large number of tests sold per year (> 28 million). BEC defines the occurrence of 1-4 annual discrete events for the potentially hazardous situation as a Remote occurrence.

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If annual discrete events = 1 to 4 (Low incidence rate)

1. Investigate root cause (e.g., sample handling, contamination, drug interference, heterophile, etc.)
2. Update risk assessment based on event if appropriate
3. Determine CAPA eligibility and potential corrective action(s) (see **Table 1-1** below)
4. Continue post-launch surveillance

If annual discrete events ≥ 5 (High incidence rate)

1. Conduct Post Launch Risk Assessment
2. Determine CAPA eligibility
3. Determine Product Corrective Action eligibility
4. Notify FDA
5. Continue root cause investigation
6. Extend ERT post-launch surveillance

For this approach, a discrete event is defined as a customer complaint resulting in confirmed thermally insensitive sample(s) yielding falsely increased or decreased result(s) where the increase or decrease is proven to be caused by inappropriate adjustment of the thermal algorithm (residual thermal bias). Specifically, one discrete event would represent one malfunction, which may have resulted in more than one erroneous patient result. Although the malfunction may result in more than one customer complaint, if it is tied to one malfunction event, then it is counted as one discrete event.

The actual corrective action(s) depend on the frequency, magnitude, severity, and root cause. Several potential outcomes are possible, and would be driven by the risk assessment and CAPA. Examples of potential corrective actions are identified in **Table 1-1** below:

Table 1-1: Potential Corrective Actions in Event of Failure

Frequency	Potential Corrective Action
Low incidence (1-4 discrete events)	Customer communication and/or Labeling Change • Technical Bulletin • Important Product Notification • Labeling change (updates to IFU) • Design Change
High incidence (≥ 5 discrete events)	All of the above plus… Product CAPA Product Corrective Action escalation Communication to FDA

The AccuTnI+3 ERT process will rapidly identify and address any product performance issues experienced by customers, including thermally insensitive samples should they occur. This process is directed by and staffed with subject matter experts who have been intimately involved in the development of the thermal algorithm and the AccuTnI+3 reagents, and customer support of the current troponin assay. BEC is committed to this plan to ensure that appropriate action is taken in the event of any AccuTnI+3 performance failure.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Question 2: Limit of quantitation (LoQ)

FDA: Please provide an explanation for the difference in the performance of sample 4 depending on the instrument used (please refer to FDA's Calculation of Within-Lab Standard Deviation and %CV for Each Instrument). We are concerned that the %CV for this sample doubled (from 15% to 30%) depending on the instrument that was used. Again, please provide this information by Wednesday June 12, 2013 at 2:00 P.M.

FDA's Calculations of Within-Lab Standard Deviation and %CV for Each Instrument

Instrument	Sample ID	Mean	SD	%CV
402603	4	0.025	0.007	30%
502884	4	0.027	0.005	19%
507310	4	0.026	0.004	15%

BEC Response to Question 2

BEC calculations of within-laboratory standard deviation yield slightly different, but similar values to those calculated by the Agency (See **Table 2-1**):

Table 2-1: Within-Lab Standard Deviation and %CV of Sample 4 by Instrument

Instrument	Sample ID	Mean	SD	%CV
402603	4	0.025	0.0067	26%
502884	4	0.027	0.0047	18%
507310	4	0.026	0.0038	15%

Imprecision estimates are subject to variability much like individual replicates. A distribution of imprecision measurements is expected when the same sample is evaluated on numerous occasions and under multiple conditions. The result for Instrument 402603 above can likely be attributed to the random variability associated with imprecision estimates. This random variability cannot be distinguished from systematic variability associated with a particular variable based on this data alone. Other samples in the Limit of Quantitation (LoQ) study demonstrate lower or equivalent imprecision on Instrument 402603 when compared to the other two instruments (see **Table 2-2** for two examples), further supporting the hypothesis of random rather than systematic differences in imprecision.

Table 2-2: Within-Lab Standard Deviation and %CV of Samples 2 and 11 by Instrument

Instrument	Sample ID	Mean	SD	%CV
402603	2	0.014	0.0033	24%
502884	2	0.016	0.0050	31%
507310	2	0.014	0.0035	26%
402603	11	0.037	0.0025	7%
502884	11	0.035	0.0029	8%
507310	11	0.034	0.0023	7%

Creating a precision profile using multiple samples in the derivation of LoQ provides a robust estimation of imprecision at specified concentrations while reducing the impact of random variability observed for individual samples. When results for all samples in the Limit of Quantitation (LoQ) study are evaluated, rather than a single sample on a single instrument, the precision profile approach as specified in Appendix D of CLSI EP17-A2 yields a 20% CV LoQ of 0.02 ng/mL. This same conclusion is reached regardless of whether the study is evaluated instrument by instrument, reagent lot by reagent lot, or run temperature by run temperature.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Callaghan, Jim
Sent: Wednesday, June 12, 2013 7:52 AM
To: Caposino, Paula
Subject: RE: Information for DS for instrument that we are getting ready to clear.

I would only put in the stuff in bold plus what you have under Systems Descriptions. You should also include the Troponin description

Jim

From: Caposino, Paula
Sent: Tuesday, June 11, 2013 6:55 PM
To: Callaghan, Jim
Subject: Information for DS for instrument that we are getting ready to clear.

Hi Jim,
I am preparing the DS for the Access 2 Immunoassay System that will most likely be cleared with troponin from Beckman Coulter. I was hoping you would look at this information that I want to put in the DS for the analyzer. Is this too much? Is it not enough? Let me know if I am in the ballpark. Thanks.
Paula

Device description:

The Access 2 Immunoassay System is a microcomputer controlled, random-access and continuous-access instrument. The instrument performs enzyme immunoassays utilizing paramagnetic particle solid phase and chemiluminescent detection. A luminometer measures the amount of light generated by the reaction. The Access 2 is designed to be used with numerous different immunoassays. The system software was designed such that immunoassays can be added to the system without changing the system software. A separate assay-specific protocol file, the APF, is loaded into the system. The APF contains all assay specific parameters used to process a particular assay including:

- Identification of reagents used to process the assay
- The sequence and volumes of the sample and reagent additions
- Mixing parameters
- Incubation times
- Math model used to convert the measured response to a reportable result
- Calibration information
- Thermal algorithm

The major Access 2 Immunoassay System components which execute all system processing, control and interface functions are listed below:

- Carousel Module
- Pipettor Module
- Analytical Module
- Fluidic Module
- Electronic/Systems Computer
- Peripheral Module

Systems Descriptions:

259

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1. Modes of Operation:
   Micro computer controlled analyzer with random and continuous access.

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?
   Yes __X___ or No ____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?
   Yes _____ or No __X__

2. Software:
   FDA reviewed applicant's Hazard Analysis and software development processes for this line of product types:.
   Yes __X___ or No _____

3. Specimen Identification:
   Bar code or sample information can also be entered manually.

4. Specimen Sampling and Handling:
   Instruction on sample handling is provided in the reagent labeling.

5. Calibration:
   An active calibration curve is required for all tests. For the Access AccuTnI assay, calibration is required every 56 days.

6. Quality Control:
   The sponsor recommends that at least two levels of an appropriate quality control material be tested a minimum of once a day. The sponsor also states that quality control testing should be performed in accordance with laboratory accreditation requirements, applicable laws and good laboratory practices.

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160
Fax. (301) 847-8513

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Caposino, Paula

From: Oetter, Kerrie S <ksoetter@beckman.com>
Sent: Monday, June 10, 2013 2:47 PM
To: Caposino, Paula
Cc: Cundy, Scott T
Subject: RE: Beckman Coulter response to k121214 June 7 AI Request

Importance: High

Dear Paula,

Please call – 4pm Eastern Time

Toll-free dial-in number (U.S. and Canada):
(866) 548-3459

Conference code:
276 553 7316

Beckman Coulter Employees that will be on the teleconference:

Scott Cundy, Vice President Regulatory Affairs and Quality

Kerrie Oetter, Senior Regulatory Affairs

Kathy Horsfall, Senior Program Manager

Corey Carlson, Development Manager

Eric Hjelm, Staff Application Scientist

Marion Navratil – Senior Manager Development

Thanks,
Kerrie Oetter

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, June 10, 2013 12:59 PM
To: Cundy, Scott T
Cc: Oetter, Kerrie S
Subject: FW: Beckman Coulter response to k121214 June 7 AI Request
Importance: High

Dear Scott,

Thank you for the information that you provided to me this morning.

After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency

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needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

We would also like to schedule a teleconference with you for today to discuss this request. Let me know what time you are available.

Thank you very much,

Paula

P.S., I will follow up this email with a question regarding your LoQ analyses from our Statisticians.

262

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Caposino, Paula

From: De, Arkendra
Sent: Monday, June 10, 2013 2:00 PM
To: Caposino, Paula
Subject: RE: Follow up question for Beckman. Does this get to the point?

Yes, it gets to the point. Looks good

Arkendra

From: Caposino, Paula
Sent: Monday, June 10, 2013 1:58 PM
To: De, Arkendra
Subject: Follow up question for Beckman. Does this get to the point?

Dear Kerrie,

Please provide an explanation for the difference in the performance of sample 4 depending on the instrument used (please refer to FDA's Calculation of Within-Lab Standard Deviation and %CV for Each Instrument). We are concerned that the %CV for this sample doubled (from 15% to 30%) depending on the instrument that was used. Again, please provide this information by Wednesday June 12, 2013 at 2:00 P.M.

FDA's Calculations of Within-Lab Standard Deviation and %CV for Each Instrument

Instrument	Sample id	Mean	SD	%CV
402603	4	0.025	0.007	30%
502884	4	0.027	0.005	19%
507310	4	0.026	0.004	15%

Thank you in advance for your response.

Regards,

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
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Building 66, Room 5648
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Caposino, Paula

From: Pilcher, Ian
Sent: Monday, June 10, 2013 12:48 PM
To: Caposino, Paula; Chesler, Ruth A
Subject: RE: Corrective Action Plan request from Beckman--Please read for adequacy????

looks good to me.

Ian

From: Caposino, Paula
Sent: Monday, June 10, 2013 12:40 PM
To: Pilcher, Ian; Chesler, Ruth A
Subject: Corrective Action Plan request from Beckman--Please read for adequacy????
Importance: High

Dear Scott and Kerrie,

Thank you for the information that you provided to me this morning.

After discussing the response with the review team, we have the following request. In your response to question 1(a), you explain that "if a sample that was thermally insensitive led to an anomalous result, the Access 2 system software would have recorded the data necessary to understand that result. We believe that the anomalousness of such a result, backed by the ability to record and recover relevant data, would quickly come to our attention by virtue of our complaint investigation process". To fully resolve this deficiency, the Agency needs to understand exactly what you will do if you identify that the corrective algorithm has failed. Please clearly explain the corrective action that you will implement if an anomalous test result is identified. Please specify the threshold in anomalous test results that will trigger the corrective action. Please be very specific in your description of the corrective action. Be advised that we do not believe that opening an investigation based on the anomalous result is sufficient. Please provide this detailed corrective action plan to me no later than Wednesday June 12, 2013 at 2:00 P.M. EST.

We would also like to schedule a teleconference with you for today to discuss this request. Let me know what time you are available.

Thank you very much,

Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD
10903 New Hampshire Avenue
Building 66, Room 5648
Silver Spring, MD 20993
Tel. (301) 796-6160

265

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Fax. (301) 847-8513

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Caposino, Paula

From: De, Arkendra
Sent: Monday, June 10, 2013 10:56 AM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse
Attachments: FDA Plasma Calculations for K121214.doc

Thanks Paula. I just saw that Beckman sent in the response for the questions we had on Friday of last week. Attached are calculations that I did using only the plasma measurements.

A few things I noticed:
1. Page 28 of the Sponsor's May 3, 2013 response doesn't make sense to me. The %CV listed in table 13-3 on page 28 doesn't match the calculated results.
What I mean is that when dividing the standard deviation by the mean and multiplying by 100, using the numbers in the table, the %CV result is not the same as the %CVs depicted in the table.
2. The calculated results from me differs from the sponsor's table 13-3 on page 28 (referring to same response as number 1). As it turns out, the sponsor did something different (haven't gotten a chance to look at it in detail).
3. There are statistically significant differences in the variance when comparing across instruments at 28 C run temperature. These are in the attachment.

Arkendra

From: Caposino, Paula
Sent: Monday, June 10, 2013 9:12 AM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Sorry Arkendra,
I just got this. The Q2 is likely the plasma measurements and the Q6 is in serum.
Thanks,
Paula

We could just focus on plasma.

267

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FDA's Calculations of Within-Lab Standard Deviation and %CV for Each Instrument

Used only plasma data for all calculations

Instrument 402603

Sample ID	Mean	SD (across instruments, sites, temperature, runs, days, replicates)	%CV
1	0.011	0.005	45%
2	0.014	0.005	36%
3	0.023	0.006	26%
4	0.025	0.007	30%
5	0.038	0.003	7.89%
6	0.039	0.003	7.69%
7	0.053	0.003	5.66%
8	0.064	0.006	9.38%
9	0.142	0.007	4.93%
10	0.264	0.0164	6.21%
11	0.037	0.003	8.11%

Instrument 502884

Sample ID	Mean	SD (across instruments, sites, temperature, runs, days, replicates)	%CV
1	0.013	0.004	31%
2	0.016	0.005	31%
3	0.023	0.006	26%
4	0.027	0.005	19%
5	0.037	0.003	8.11%
6	0.037	0.003	8.11%
7	0.053	0.003	5.66%
8	0.062	0.005	8.06%
9	0.134	0.007	5.22%
10	0.247	0.009	3.64%
11	0.035	0.003	8.57%

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Instrument 507310

Sample ID	Mean	SD (across instruments, sites, temperature, runs, days, replicates)	%CV
1	0.011	0.004	36%
2	0.013	0.004	31%
3	0.022	0.006	27%
4	0.026	0.004	15%
5	0.036	0.003	8.33%
6	0.037	0.003	8.11%
7	0.053	0.004	7.55%
8	0.063	0.005	7.94%
9	0.138	0.007	5.07%
10	0.250	0.010	4.00%
11	0.034	0.003	8.82%

Instrument/Temperature Combination Within-Lab Standard Deviations

	Instrument 402603, Run Temp 28 C Within-Lab Standard Deviaiton	Instrument 502884, Run Temp 28C Within-Lab Standard Deviaiton	Instrument 507310, Run Temp 28 C Within-Lab Standard Deviaiton
Sample 1*	0.002	0.005	0.004
Sample 2*	0.004	0.008	0.005
Sample 3	0.008	0.007	0.008
Sample 4*	0.009	0.007	0.005
Sample 5	0.003	0.003	0.003
Sample 6	0.003	0.003	0.003
Sample 7*	0.002	0.003	0.004
Sample 8	0.004	0.004	0.004
Sample	0.006	0.008	0.005

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9*			
Sample 10*	0.015	0.007	0.0096
Sample 11	0.002	0.003	0.003

*Indicates that the variance of these samples differs across instruments in a strongly statistically significant sense (using Bartlett's test for testing equality of variances)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: Kerrie Oetter <koetter@live.com>
Sent: Monday, June 10, 2013 10:21 AM
To: Caposino, Paula
Cc: ksoetter@beckman.com; stcundy@live.com
Subject: Beckman Coulter response to k121214 June 7 AI Request
Attachments: k121214 response to June 7 AI request.pdf; Appendix 1.pdf

Dear Paula,

Attached is our response to your request dated June 7, 2013, for k121214. You will find the response and revised IFU attached. I am sending the response through my personal e-mail, since the Beckman Coulter Outlook is currently out of service.

Please let me know if you have any questions.

Thanks,
Kerrie Oetter
ksoetter@beckman.com / 952-368-7858

271

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BECKMAN COULTER.

Responses to FDA's June 7, 2013 Request for Additional Information (Fourth AI Letter)

Question 1: Limit of quantitation (LoQ)

FDA: In response to question 13(a), you state "for each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated..." Can you please specify the components of variance that went into within-run and between-run? Did you include the across days variability? For the data by run temperature, can you explain how/if you incorporated the different instruments and lots into the within laboratory %CV?

BEC Response to Question 1

Within each run temperature, three instruments were each calibrated at three different temperatures, providing nine testing scenarios. The data from each scenario's set of 60 replicates (3 days of 2 runs per day with 10 replicates each run) was analyzed using a general linear model as specified in CLSI EP5-A2. This nested analysis of variance (ANOVA) had troponin in ng/mL as the dependent variable and the following independent variables: day and run nested within day. The resultant run and day variances were added together to obtain between-run variance. The residual variance (within-run) was added to the between-run variance to obtain the within-laboratory variance.

For each sample, the within-laboratory variances and mean values from all nine scenarios were averaged. The coefficient of variation (CV) was computed for each sample by first taking the square root of its within-laboratory variance to obtain standard deviation and then dividing by the average mean value. The resultant precision profile analysis using the mean and %CV for each sample provided an estimate of 10% LoQ at 0.04 ng/mL and 20% LoQ at 0.02 ng/mL for troponin in the same manner as Appendix D in CLSI EP17-A2.

Question 2: Limit of quantitation (LoQ)

FDA: Can you please provide the results of the regression analysis for the study comparing lithium heparin plasma samples and serum samples randomly selected from among the entire pivotal trial cohort in singlicate excluding all samples under the LoQ of your device?

BEC Response to Question 2.

The Pivotal Trial Cohort data have been analyzed following exclusion of samples with troponin values below AccuTnI+3 assay's LoQ; the following exclusion of those samples, is provided in Table 2-1 below:

Table 2-1: AccuTnI+3 Access 2, Serum vs Plasma, Passing Bablok

Range (ng/mL)	N	Slope (95% CI)	Intercept (95% CI)	Correlation
0.02 - 20	96	1.00 (0.98 – 1.00)	0.00 (0.00 – 0.00)	r = 1.00

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Question 3: Field Effectiveness Study

FDA: Can you explain why the results of sample MORE 1 provided in table 2-3 "More 1 Precision Results from the Field Effectiveness Study" from site S on lot 2 do not appear to support your current LoQ claim? Specifically, the mean result obtained by the site based on a sample size of 40 was 0.022 ng/mL with a %CV of 29.1. We are concerned that these data demonstrate that at 0.02 ng/mL, your device may not consistently provide results with the claimed %CV of less than 20%. Please provide an explanation for these results.

BEC Response to Question 3

A number of complex, well-controlled studies were conducted to establish our LoQ claims including those described in the response to question 1 above. These studies used patient samples as recommended in EP17-A2. Results from the analyses of the studies carried out in accordance with EP17-A2 demonstrate that the 20% LoQ is 0.02 ng/mL.

The External Field Effectiveness study was designed to evaluate the precision of three AccuTnI+3 reagent lots in multiple laboratories over multiple days/runs, in the hands of clinical laboratory technologists. Results were intended to provide additional confidence that the final AccuTnI+3 product in its entirety—including thermal algorithm, system software, assay protocol files, etc.—performs properly on fielded instruments.

The samples used in the Field Effectiveness study were commercial quality controls (QC) that are intended to reflect the behavior of natural patient samples and thus yield results that are predictive of results from patient specimens. We used commercial QC in the Field Effectiveness study because our customers would typically use these kinds of controls to assess the assay's precision performance and to detect performance issues on a daily basis before testing patient specimens. By using commercial QC in the Field Effectiveness study, we evaluated the performance of the device as our customers would and as it is intended to be used in the field.

Our analysis of results from this study showed that the precision acceptance criteria were met for each of the six QC samples tested at five external laboratories using three lots of reagents. The current question focuses on results provided in Table 2-3 of our most recent supplemental response. That table, reproduced below, contains the MORE QC level 1 results from the Field Effectiveness study where each site performed a multiday analysis of precision with each of three reagent lots, yielding fifteen sets of results including mean TnI concentration, % CV and standard deviation.

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As shown in Table 2-3, 12 of the 15 mean TnI concentrations for the MORE 1 QC sample fall below 0.02 ng/mL, indicating that the actual concentration of the specimen is below 0.02 ng/mL.

Table 3-1: MORE 1 Precision Results from the Field Effectiveness Study

Site	Sample	Lot	n	Concentration (ng/mL)	CV	SD
U	MORE 1	1	40	**0.016**	20.6%	0.0033
A	MORE 1	1	80	0.020	20.5%	0.0041
S	MORE 1	1	40	**0.011**	52.7%	0.0058
Q	MORE 1	1	40	0.023	5.7%	0.0013
E	MORE 1	1	36	**0.016**	31.3%	0.0050
U	MORE 1	2	40	**0.013**	20.8%	0.0027
A	MORE 1	2	62	**0.010**	28.0%	0.0028
S	MORE 1	2	40	0.022	29.1%	0.0064
Q	MORE 1	2	40	**0.018**	14.4%	0.0026
E	MORE 1	2	36	**0.013**	38.5%	0.0050
U	MORE 1	3	40	**0.010**	16.0%	0.0016
A	MORE 1	3	62	**0.010**	32.0%	0.0032
S	MORE 1	3	40	**0.010**	45.0%	0.0045
Q	MORE 1	3	40	**0.017**	12.9%	0.0022
E	MORE 1	3	36	**0.010**	35.0%	0.0035

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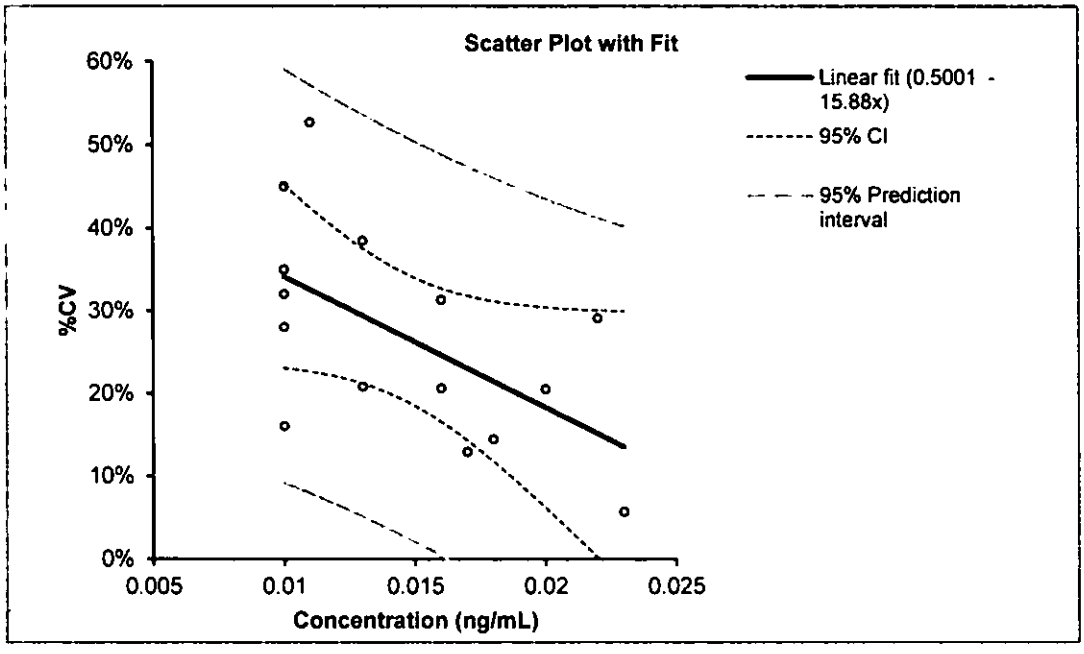
We also provided findings from a precision profile analysis based on CV using all of the MORE I data in the most recent supplemental response. It is important to note that by using a precision profile approach as specified in Appendix D of CLSI EP17-A2 a regression analysis shows a significant relationship between concentration and %CV (p=0.025). This analysis takes into account information from all of the observations rather than just a single observation. Results from the precision profile (Figure 2-1 shown below) showed a calculated precision of 18.3% CV at 0.02 ng/mL.

Figure 3-1: Precision Profile



These data support our conclusion that the 20% LoQ of the AccuTnI+3 assay on the Access 2 is 0.02 ng/mL. In light of the extensive evidence we have provided based on results from native patient samples and commercial controls, results from the one data set in question can be attributed to random variation.

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BECKMAN COULTER.

Question 4: Linearity

FDA: Your acceptance criteria for samples with troponin concentrations less than 0.075 ng/mL for maximum deviation from linearity is 0.012 ng/mL. Meanwhile you state "in the new low-range linearity studies, the maximum deviation from linearity was 1%." Your current acceptance criterion for linearity for samples less than 0.075 ng/mL is unacceptable broad (allowable nonlinearity of ± 60% at 0.02 ng/mL, ± 40% at 0.03 ng/mL and ± 30% at 0.04 ng/mL). Based on your data (maximum observed non-linearity is 1% in the new low-range linearity studies) you can tighten this criteria. Please tighten the criteria for allowable maximum deviation from linearity for samples less than 0.075 ng/mL (We recommend no more than +-15%).

BEC Response to Question 4

The criteria will be tightened to a maximum allowable deviation from linearity of ≤15% across the entire assay range. The product instruction for use (IFU) has been updated to reflect these tightened criteria. A copy of the revised Instructions for Use (IFU) is attached in Appendix 1.

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Appendix 1: Device labeling (Instructions for Use, IFU)

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[13] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)
Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.

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- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. Access 2
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since

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obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]

Access AccuTnI+3 Result (X) on Access 2	Report result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result < 0.01 ng/mL
0.01 ng/mL (LoD) ≤ X < 0.02 ng/mL (20% CV LoQ)	X ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% CV LoQ)	X ng/mL
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

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Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

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Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94 – 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

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In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

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Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of ≤ 15%.

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

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Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

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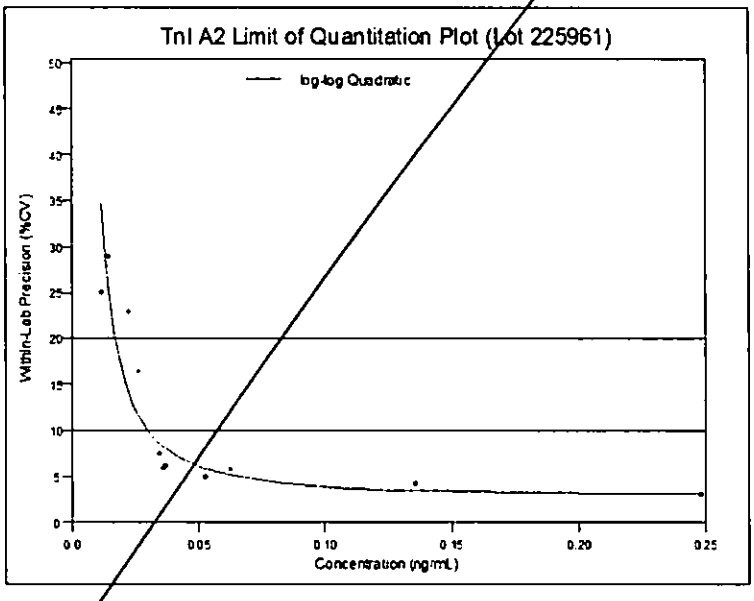
Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Caposino, Paula

From: De, Arkendra
Sent: Friday, June 07, 2013 6:51 PM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Paula,

As I was looking at the Excel file, I noticed that there are two tabs in the spreadsheet related to LoQ.
One of them is "Q2 Lmts of Detection (LoD-LoQ)" , and the other is "Q6 Matrix Comp (Serum LoD-LoQ)".
Could you tell me what these refer to and what the difference is between these two?
Should I use both tabs when analyzing the data?

Thanks,
Arkendra

From: Caposino, Paula
Sent: Friday, June 07, 2013 11:02 AM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Perfect. I'll talk to you then.

I would like to confirm that the sponsor's power function model by run temperature (just 28 degrees) is correct for both serum and plasma.

From: De, Arkendra
Sent: Friday, June 07, 2013 11:00 AM
To: Caposino, Paula
Cc: Meier, Kristen L.
Subject: RE: Beckman Troponin REsponse

Paula,

Kristen and I talked earlier, and we were thinking of meeting with you at 1:30 pm today.
Does that work for you? We also were thinking of gathering at Kristen's office (for those in White Oak) for the meeting.
Please let me know.

Thanks,
Arkendra

From: Meier, Kristen L.
Sent: Friday, June 07, 2013 10:40 AM
To: Caposino, Paula
Cc: De, Arkendra
Subject: RE: Beckman Troponin REsponse

293

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Thanks Paula – when Arkendra starts working we can see what time works for him.
Arkendra – one thing we want to do with the Excel file is just get a better understanding of the study design they used...

Kristen

From: Caposino, Paula
Sent: Friday, June 07, 2013 10:31 AM
To: Meier, Kristen L.; De, Arkendra
Subject: RE: Beckman Troponin REsponse

Here it is.
Thanks.
I'm free for the rest of the day so let me know when you want me to come down.
Paula

From: Meier, Kristen L.
Sent: Friday, June 07, 2013 10:04 AM
To: Caposino, Paula; De, Arkendra
Subject: RE: Beckman Troponin REsponse

Hi Paula – if you can email the excel file that would be a huge help. I have a sponsor telecom 11-12 but could talk after that (say 1:00?) if Arkendra is free (he is west coast time and will log in soon) –I hope to leave by 2 today since I am going out of town this eve. Are you in the office? We can both call him from here or use his call in if you are not at WO.

Kristen

From: Caposino, Paula
Sent: Friday, June 07, 2013 9:59 AM
To: De, Arkendra
Cc: Meier, Kristen L.
Subject: Beckman Troponin REsponse

Can you please review the following:
Response 1b
Response to question 13—this is the LoQ question. There is some additional information in response 2 that you may want to look at. We asked question 13 when we reviewed the response to question 2.

My question to you is, can they support a 20% CV claim at 0.02.

The line data for the LoQ study is in IMAGE (k121214) listed as Statistical data. Let me know if you need me to email this to you.

Can we chat at some point today?

Thanks,
Paula

Paula Velasco Caposino, Ph.D.
Scientific Reviewer
Food and Drug Administration
CDRH, OIR, DCTD

294

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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10903 New Hampshire Avenue
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K121214/S002

BECKMAN COULTER

FDA CDRH DMC
JUN 06 2013
Received

June 4, 2013

Paula Velasco Caposino, Ph.D.
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center-W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-002

RE: 510(k) #k121214, k121214-S001, and Letter of May 3, 2013
Access AccuTnI+3 on the Access 2 Immunoassay Systems

Dear Dr. Caposino:

This communication responds to questions and concerns expressed by FDA in its k121214-S001 ("Second AI Letter") and May 3, 2013 request for additional information ("Third AI Letter"). All correspondence described above applies to BEC's April 20, 2012 Section 510(k) premarket notification ("Submission," or "original Submission"), k121214, of intent to market the Access AccuTnI, now referred to as Access AccuTnI+3, on the Access 2 Immunoassay Systems.

BEC has responded to each point FDA ("FDA" or "the Agency") raised in the Second AI Letter and Third AI Letter and has organized the body of these responses ("Response") according to each question. Each numbered BEC response addresses a numbered FDA question or concern; it is prefaced by the corresponding text from each of the AI Letters. Each of FDA's numbered items in theses AI Letters are designated as a "question" and is referenced within this Response as Question 4, Question 7(d), etc. The Third AI Letter also contains two additional email questions. These two questions were added as questions 12 and 13.

Throughout these responses, reviewers are referred to numbered appendices. The appendices contain requested data, supplementary tables and figures, and document revisions, including the Instructions for Use ("IFU").

The eCopy of this Response is an exact duplicate of the paper copy except that line data referred to in the Response were only provided in the eCopy. A placeholder was provided in our Second and Third AI Letter Response and to Question 1 (Thermal sensitivity), Question 2 (Limits of detection), Question 3 (Linearity), and Question 6 (Clinical matrix comparison study) of the paper copy referring back to the eCopy for that information.

If there are questions regarding this Response, you may contact me by telephone at (952) 368-7858, by fax at (952) 368-7610, or by e-mail at ksoetter@beckman.com. Our letter identifying Kerrie Oetter as the new correspondent for this file is attached to our Third AI Letter Response as Appendix 7.

Sincerely,

Kerrie Oetter

Kerrie S. Oetter
Senior Regulatory Affairs Analyst

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BECKMAN COULTER®

June 4, 2013

Paula Velasco Caposino, Ph.D.
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center-W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-002

RE: 510(k) #k121214, k121214-S001, and Letter of May 3, 2013
Access AccuTnI+3 on the Access 2 Immunoassay Systems

Dear Dr. Caposino:

This communication responds to questions and concerns expressed by FDA in its k121214-S001 ("Second AI Letter") and May 3, 2013 request for additional information ("Third AI Letter"). All correspondence described above applies to BEC's April 20, 2012 Section 510(k) premarket notification ("Submission," or "original Submission"), k121214, of intent to market the Access AccuTnI, now referred to as Access AccuTnI+3, on the Access 2 Immunoassay Systems.

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Throughout these responses, reviewers are referred to numbered appendices. The appendices contain requested data, supplementary tables and figures, and document revisions, including the Instructions for Use ("IFU").

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If there are questions regarding this Response, you may contact me by telephone at (952) 368-7858, by fax at (952) 368-7610, or by e-mail at ksoetter@beckman.com. Our letter identifying Kerrie Oetter as the new correspondent for this file is attached to our Third AI Letter Response as Appendix 7.

Sincerely,

Kerrie Oetter

Kerrie S. Oetter
Senior Regulatory Affairs Analyst

Enclosure

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BECKMAN COULTER

Responses to FDA's January 8, 2013 Request for Additional Information (Second AI Letter)

BEC has responded to each question or concern FDA ("FDA" or "the Agency") raised in its January 8, 2013 request for additional information ("Second AI Letter") and has organized the body of this response ("Response") according to the 12 numbered sections/questions in the Second AI Letter. Each numbered BEC response addresses a numbered FDA question or concern; it is prefaced by the corresponding text from the Second AI Letter. Each of FDA's 12 numbered items in the Second AI Letter is designated as a "question" and is referenced within this Response as Question 2(a)(i), Question 5(b), etc.

In each of our responses to FDA's questions and concerns, we have provided data and discussion to show that BEC has:

- Resolved thermal sensitivity of Access AccuTnI+3 on the Access 2 Immunoassay Systems;
- Established the equivalence of serum and lithium heparin plasma as sample matrices for AccuTnI+3;
- Tightened the acceptance criteria for analytical performance of AccuTnI+3 in the areas of precision, linearity, and stability; and
- Demonstrated through our analysis of clinical and analytical data that with the introduction of the thermal algorithm, AccuTnI+3 is safe and effective.

Throughout this Response, reviewers are referred to numbered appendices. The appendices contain requested data, supplementary tables and figures, and device labeling, including the Instructions for Use ("IFU").

Finally, during a face-to-face meeting with FDA reviewers and managers on February 4, 2013 (See Appendix 1), BEC confirmed that we had not identified a root cause for the anomalous temperature concordance study described in the Submission. In the intended use setting, if aberrant sample thermal sensitivity is suspected, BEC has mechanisms in place within our complaint handling process to investigate the complaint and identify the failure mode. We are able to differentiate sample results demonstrating reduced thermal sensitivity from other potential causes of erroneous results. Access 2 system software version 3.3 records all of the parameters required for thermal adjustment of patient results. Using these recorded parameters, we can compare the adjusted and unadjusted sample results to determine if the sample demonstrated thermal insensitivity.

This Response incorporates the results from multiple new studies at BEC, the reanalysis of data from previous, comprehensive studies, and outcomes of discussions with the Agency's team of reviewers.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 1: Thermal sensitivity

FDA: In your response to item 1a from our letter requesting additional information dated June 20, 2012, you provided new studies and data from existing studies to demonstrate that your corrective algorithm resolved the temperature sensitivity issue of your device. We have the following concerns with your response:

(1)(a) FDA (Concordance Study): In the new studies that you performed (and in the data from the low dose samples of the original method comparison study and the pre-verification concordance study), you only evaluated the performance of the device at the temperature extremes. During our October 26, 2012 face-to-face meeting we requested that you evaluate any new data in support of your corrective algorithm at different temperatures spanning the operational temperature range of your device (i.e., not only comparing the performance at the extreme temperatures). However, you only provided data at different temperatures for the concordance analysis for the new concordance study. Therefore, please provide Passing Bablok analyses for all studies in support of your corrective algorithm at different temperatures spanning the operational temperature range of your device (i.e., not only comparing the performance of the device at extreme temperatures). Please make sure that these analyses are performed using singlicate results (in accordance with the intended use of your device). Please provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analyses. You should also provide a table with the proportion of observations above the cut-off at each temperature for FDA review. Please note that for the new concordance study, two thirds of the samples had values above the 0.03 ng/mL cut-off while in the original concordance study that demonstrated unacceptable bias, half of the observations had troponin values above the 0.03 ng/mL cut-off. We are very concerned that the study design for the new concordance studies may not be equivalent to the study design of the original concordance study because the observations in the new studies may have higher troponin values than the original study. You may need to repeat your concordance studies closely mimicking the design of the original concordance study to demonstrate that you have resolved the temperature bias issue.

BEC Response to Question 1(a).

As requested by FDA, Passing-Bablok analyses are provided for Access AccuTnI+3 on the Access 2 Immunoassay Systems at different temperatures spanning the operational temperature range of the device, i.e., not only comparing the performance of the device at temperature extremes. Analyses were performed on singlicate results from multiple studies, and estimates of slopes and intercepts and their associated 95% confidence intervals are provided for all regression analyses. Furthermore, the proportion of observations above the 0.03 ng/mL cutoff at each temperature is reported. **Table 1-1** below provides these results for four independent studies.

Table 1-1: Passing-Bablok Analysis of Singlicate Results at Incremental Temperatures

Study	Low Temp	High Temp	N	Slope	Slope 95% CI	Intercept	Intercept 95% CI	R^2	Low Temp % >0.03 ng/mL	High Temp % >0.03 ng/mL
Pre-verification Concordance Study	18 °C	26 °C	98	1.07	(1.04, 1.10)	0.00	(0.00, 0.00)	0.98	52%	59%
	18 °C	22 °C	100	1.01	(1.00, 1.03)	0.00	(0.00, 0.00)	0.99	53%	55%
	22 °C	26 °C	98	1.06	(1.05, 1.08)	0.00	(0.00, 0.00)	0.99	54%	59%
	20 °C	28 °C	100	1.00	(0.96, 1.03)	0.00	(0.00, 0.00)	0.98	58%	61%
	20 °C	24 °C	100	0.99	(0.97, 1.01)	0.00	(0.00, 0.00)	0.99	58%	61%
	24 °C	28 °C	100	1.01	(0.99, 1.04)	0.00	(0.00, 0.00)	0.99	61%	61%
Thermal Sensitivity – Impact on Low Dose Concordance/Agreement: Repeat Study	18 °C	26 °C	109	0.95	(0.93, 0.98)	0.00	(0.00, 0.00)	0.97	66%	71%
	18 °C	22 °C	108	0.99	(0.97, 1.00)	0.00	(0.00, 0.00)	0.98	66%	65%
	22 °C	26 °C	108	0.97	(0.95, 0.99)	0.00	(0.00, 0.00)	0.99	65%	70%
	20 °C	28 °C	110	0.98	(0.95, 1.00)	0.00	(0.00, 0.00)	0.99	66%	73%
	20 °C	24 °C	110	1.00	(0.98, 1.02)	0.00	(0.00, 0.00)	0.99	66%	71%
	24 °C	28 °C	110	0.97	(0.95, 1.00)	0.00	(0.00, 0.00)	0.99	71%	73%
Additional Concordance Studies - Overall	18 °C	28 °C	433	0.96	(0.95, 0.97)	0.00	(0.00, 0.00)	0.99	81%	86%
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Low Dose***	18 °C	28 °C	48	1.02	(0.98, 1.06)	0.00	(0.00, 0.00)	0.99	N/A	N/A
	18 °C	23 °C	48	0.98	(0.94, 1.01)	0.00	(0.00, 0.00)	0.99	N/A	N/A
	23 °C	28 °C	48	1.04	(1.02, 1.07)	0.00	(0.00, 0.00)	0.99	N/A	N/A
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Full Range***	18 °C	28 °C	108	0.98	(0.98, 0.99)	0.00	(0.00, 0.00)	1.00	N/A	N/A
	18 °C	23 °C	108	1.01	(1.00, 1.03)	0.00	(0.00, 0.00)	1.00	N/A	N/A
	23 °C	28 °C	108	0.97	(0.95, 0.98)	0.00	(0.00, 0.01)	0.99	N/A	N/A

Note: "N/A" = Not applicable as results are primarily above 0.03 ng/mL.

Such an analysis of intermediate, incremental temperatures was also possible using data from the original Thermal Sensitivity-Robustness study described in the Submission. While this study represents a substantially smaller sample size, it did include five commercial controls, three patient pools, and two TnI spiked samples. Numerous incremental temperatures were represented, and a Passing-Bablok regression analysis was performed. This analysis was performed on singlicate measurements, and **Table 1-2** displays these results. Note that the slightly wider confidence intervals are due to the smaller sample size.

Table 1-2: Passing-Bablok Analysis of Thermal Sensitivity-Robustness*

Comparison	Instrument	N	Slope	Slope 95% CI	Intercept	Intercept 95% CI	R^2
22 °C vs. 19 °C	404334	10	0.97	(0.94, 0.99)	0.00	(-0.02, 0.03)	1.00
25 °C vs. 19 °C	404334	10	0.94	(0.90, 0.97)	0.00	(-0.07, 0.10)	1.00
27 °C vs. 19 °C	404334	10	0.93	(0.89, 0.95)	0.00	(-0.05, 0.06)	1.00
25 °C vs. 22 °C	404334	10	0.97	(0.94, 0.98)	0.00	(-0.01, 0.06)	1.00
27 °C vs. 22 °C	404334	10	0.96	(0.93, 0.99)	0.00	(-0.01, 0.04)	1.00
27 °C vs. 25 °C	404334	10	0.99	(0.98, 1.00)	0.01	(0.00, 0.02)	1.00
22 °C vs. 19 °C	500000	10	0.97	(0.93, 0.98)	0.00	(-0.02, 0.01)	1.00
25 °C vs. 19 °C	500000	10	0.92	(0.89, 0.96)	0.00	(-0.02, 0.07)	1.00
27 °C vs. 19 °C	500000	10	0.92	(0.91, 0.94)	0.00	(-0.01, 0.05)	1.00
25 °C vs. 22 °C	500000	10	0.98	(0.88, 1.00)	0.00	(-0.01, 0.09)	1.00
27 °C vs. 22 °C	500000	10	0.96	(0.90, 0.98)	0.00	(-0.01, 0.05)	1.00
27 °C vs. 25 °C	500000	10	0.98	(0.97, 1.03)	0.00	(-0.03, 0.01)	1.00

* Data presented in **Table 1-2** are based on a single calibration curve generated at 23 °C.

Conclusion: In all cases, the Passing-Bablok slopes and intercepts demonstrate excellent correlation in measurements taken at different temperatures spanning the operational ambient temperature range of AccuTnI+3. This is true when comparing performance of the device at temperature extremes as well as at intermediate, incremental temperatures.

The Agency expressed concern that the percentage of samples with troponin I values above the 0.03 ng/mL cutoff differed between the original and repeat concordance studies. The study design of the repeat concordance study was identical to that of the original concordance study. The target sample request to the specimen vendors was the same for both studies, and the actual difference in concentration distribution is within the expected variability of external collections.

Samples with TnI values below 0.03 ng/mL are well represented in both the original and repeat concordance studies, and the repeat study showed excellent performance of these samples across temperatures, consistent with findings from other studies performed. Furthermore, the anomalous behavior of samples in the original concordance study also occurred in samples with TnI concentrations above 0.03 ng/mL. Therefore, the difference in distribution of the samples used for the repeat study does not account for the improved performance across temperatures. Finally, the pre-verification concordance study contained a percentage of samples with TnI concentrations below the 0.03 ng/mL cutoff very similar to that of the single anomalous study, further supporting acceptable performance of the device across temperatures. Taken together, the multiple concordance studies indicate that the temperature bias issue is resolved.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(1)(b) FDA (Concordance Study): We are still very concerned about the performance of your device. Specifically, you have not definitively explained the unacceptable bias demonstrated in the original concordance study. You have also not explained why this unacceptable performance will not be experienced by the end users of your device and will not affect the safe use of this device on patients. Please note that your discussion about the performance of the existing device without the thermal algorithm on pages 7-9 of your response cannot be used in support of the new device since these devices are not the same. Therefore, we would not anticipate the same performance once the corrective algorithm is implemented.

BEC Response to Question 1(b).

As we discussed with FDA in a face-to-face meeting on February 4, 2013 (See Appendix 1), a definitive root cause for the single anomalous concordance study has not been identified despite extensive efforts to replicate the failure and determine the root cause. While a number of potential contributors to the observed anomaly - in which many samples failed to demonstrate typical thermal sensitivity - have been proposed and tested, we have not been able to reproduce the anomalous results. Yet, the substantial number of additional datasets provided in the Submission and in our December 14, 2012 response to the First AI Letter confirms the effectiveness of the thermal algorithm and strongly indicates that the failure mode observed in the original concordance study was isolated to the sample set used for that study. Our root cause investigation report was provided as Appendix 1 in our December 14, 2012 response to the First AI Letter.

As described in the root cause investigation report, our initial hypothesis and investigation focused on aspects of pre-analytical sample handling. During the course of the investigation, we subjected freshly drawn specimens to extreme, atypical sample handling and processing conditions before testing them. We also subjected freshly drawn specimens to the handling and processing conditions described in the AccuTnI+3 Instructions for Use. In no instance did we produce samples that failed to demonstrate typical thermal sensitivity. Because end users in the clinical laboratory will routinely process and test specimens for cTnI within two hours of draw, we believe the likelihood that they will encounter thermally insensitive specimens is remote.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(1)(c) FDA (Concordance Study): In our October 26, 2012 face-to-face meeting we requested that in your response, you provide the line data from the original concordance study identifying all samples that were acquired from the vendor suspected of not handling the specimens according to your instructions for use. This information was not provided in the response. Please provide this information in support of your hypothesis that sample handling may have caused the unacceptable bias in the original concordance study.

BEC Response to Question 1(c).

We have provided the line data from the original concordance study identifying all samples that were acquired from each vendor, including the vendor (identified as "Vendor A" in the attached line data) originally suspected of inconsistent specimen handling. (See STATISTICAL DATA/k121214-S001 Line Data.zip, Tab "Q1 Thermal Sensitivity.") It is important to note that the possibility that sample handling by this particular vendor had caused or contributed to the anomalous concordance study results was a preliminary hypothesis at the time of our October 26, 2012 face-to-face meeting. However, as described in Appendix 1 of our December 14, 2012 response to the First AI Letter, additional information gathered during the root cause investigation suggested that it likely was not the primary cause. While improper sample handling cannot be entirely eliminated as a contributing factor, the investigation was not limited to this hypothesis, and all stages of sample collection, transportation, and processing were ultimately considered.

(1)(d) FDA (Calibration Strategy): In response to deficiencies 1b and 1c, you sought to establish that accuracy is not affected if the device is calibrated at a different temperature than the temperature at which the measurement is made. You reanalyze data by determining what the measurements would have been had a different calibration curve been used. In an email dated December 28, 2012 you clarified that for these studies the calibration curves were generated at the same time as the samples were measured. You concluded that regardless of calibration temperature, the difference in results met the acceptance criteria (slope term of each linear fit is either not significant or significant but has an average slope < 0.010) in all cases. However, it is not clear how it was determined whether or not the slope term of each fit was or was not significant. You should provide this information. We are concerned that a lack of significance may be indicative of an insufficient amount of data rather than a negligible slope. You should provide estimates of slopes and intercepts and their associated 95% confidence intervals for all regression analyses for FDA review.

BEC Response to Question 1(d).

The significance of the slope term of each fit in the Thermal Sensitivity-Robustness study was determined based on the probability derived from the t-ratio. The t-ratio statistic tests the null hypothesis that each regression parameter is equal to zero. It is the ratio of the parameter estimate to its standard error. If the hypothesis is true, then this statistic has a Student's t-distribution. A probability of < 0.05 indicates that the slope term is significantly different from zero. All estimated slopes were significant for linear fits performed for the Thermal Sensitivity-Robustness study analysis based on these criteria. The probabilities (Prob > |t|) indicative of significance, along with estimates of slopes, intercepts and their 95% confidence intervals, are provided below in **Table 1-3** for those analyses included in our December 14, 2012 response to Question 1.b. of the First AI Letter.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 1-3: Significance and Confidence Intervals for Thermal Sensitivity-Robustness Slopes

Calibration Temperature (°C)	Slope	Slope 95% CI	Slope Prob > |t|	Intercept*	Intercept 95% CI*	% Change/ °C	% Difference 28°C vs. 18°C
Overall	-0.005	(-0.006, -0.005)	< 0.0001	0.156	(0.142, 0.170)	-0.5	-5
16 °C	-0.005	(-0.006, -0.004)	< 0.0001	0.143	(0.111, 0.175)	-0.5	-5
19 °C	-0.005	(-0.006, -0.004)	< 0.0001	0.152	(0.120, 0.185)	-0.5	-5
22 °C	-0.005	(-0.006, -0.004)	< 0.0001	0.154	(0.121, 0.187)	-0.5	-5
25 °C	-0.005	(-0.006, -0.004)	< 0.0001	0.161	(0.127, 0.194)	-0.5	-5
27 °C	-0.005	(-0.006, -0.004)	< 0.0001	0.157	(0.124, 0.190)	-0.5	-5
30 °C	-0.006	(-0.007, -0.004)	< 0.0001	0.170	(0.136, 0.203)	-0.6	-6

* The intercepts and confidence intervals for the intercepts are provided above as requested. However, in this study, they are not meaningful because they only suggest how the device will perform at 0 °C, which is outside the instrument's labeled operating temperature range.

In specific response to Question 1(c), the calculated slopes, intercepts, and associated 95% confidence intervals for the Thermal Sensitivity-Method Comparison study are provided in **Table 1-1** above.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 2: Limits of detection

(2)(a) FDA (Limit of blank [LoB]): In your response to item 5a, you state that "to demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C, we reanalyzed all sample results from the multi-temperature LoB study data using calibration curves generated at 18°C and 28°C." However, in an email dated December 28, 2012 you stated that these calibration curves w[h]ere not the same calibration curves that were generated at the time the LoB samples were measured. For this reason, we cannot accept the reanalysis in support of your LoB results. Please perform a new LoB study to demonstrate that the LoB is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:

- *Samples (at least 4 blank samples) calibrated at 18°C and run at 18°C, 23°C, and 28°C*
- *Same samples calibrated at 23°C and run at 18°C, 23°C, and 28°C*
- *Same samples calibrated at 28°C and run at 18°C, 23°C, and 28°C*

We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline "Protocols for Determination of Limits of Detection and Limits of Quantitation" regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoB study at each calibration temperature for each lot to confirm the results of your standardized LoB study.

BEC Response to Question 2(a).

BEC has completed new studies as requested by FDA to evaluate limits of blank (LoB), detection (LoD), and quantitation (LoQ) of Access AccuTnI+3 on the Access 2 Immunoassay Systems. Line data for these studies are provided in STATISTICAL DATA/k121214-S001 Line Data.zip, Tab "Q2 Lmts of Detection (LoB)" and Tab "Q2 Lmts of Detection (LoD-LoQ)." The studies were performed by:

◊ Calibrating at 18 °C and running samples at 18 °C, 23 °C, and 28 °C
◊ Calibrating at 23 °C and running samples at 18 °C, 23 °C, and 28 °C
◊ Calibrating at 28 °C and running samples at 18 °C, 23 °C, and 28 °C

The concentrations of samples tested were selected based on the CLSI EP17-A2 guideline, with additional samples at the critical concentrations at which 10% and 20% CV are expected to be achieved.

Study protocol: Three days of testing were performed at each temperature condition on two reagent pack lots and three Access 2 instruments. For estimation of LoB, four blank samples were measured in replicates of ten on each day of testing on each instrument/reagent lot combination. For estimation of LoD, six native lithium heparin plasma samples containing low levels of troponin I analyte were measured in two runs of ten replicates each during each day of testing on each instrument/reagent lot combination. For estimation of LoQ, 11 native lithium heparin plasma samples containing low levels of troponin I analyte were measured in two runs of ten replicates each during each day of testing on each instrument/reagent lot combination.

LoB, LoD, and LoQ were each calculated using sample measurements from all three temperature conditions and all instrument/reagent lot combinations. This study design satisfies FDA's request and the requirements and recommendations of the CLSI EP17-A2 guideline, while incorporating the additional variables of calibration and run temperature. Incorporating all variables (calibration temperature, run temperature, instrument and reagent lot) introduces the greatest amount of imprecision into the analysis and results in conservative estimates of the limits of detection.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

The acceptance criteria for LoB, LoD, and LoQ were the same for all analyses and identical to those used for the original assessment described in the Submission (k121214):

◊ LoB ≤ 0.010 ng/mL
◊ LoD ≤ 0.030 ng/mL
◊ 20% LoQ ≤ 0.03 ng/mL
◊ 10% LoQ ≤ 0.06 ng/mL

The results of LoB, LoD, and LoQ as estimated by EP17-A2 and combining results from multiple temperatures are shown in **Table 2-1** and in **Figure 2-1**, **Figure 2-2**, and **Figure 2-3** below. These estimates incorporate variability from multiple reagent pack lots, instruments, and temperatures.

Note: LoQ data are presented to three decimal places for comparison purposes only. As noted in our response to Question 2(c)(ii), the default reporting units for AccuTnI+3 for the end-user are rounded to 2 decimal points (for ng/mL), and all claims in the device labeling are also shown to two decimal places.

Table 2-1: Multi-temperature LoQ Study using EP17-A2

Calibration Temperature	Measurement Temperatures (°C)	Measured LoB (ng/mL)	LoB Upper 97.5th Percentile (ng/mL)	Measured LoD (ng/mL)	Upper Bound LoD (ng/mL)	20% LoQ (ng/mL)	10% LoQ (ng/mL)
18 °C	18 °C, 23 °C, & 28 °C	0.003	0.003	0.008	0.010	0.020	0.025
23 °C	18 °C, 23 °C, & 28 °C	0.003	0.003	0.007	0.008	0.019	0.024
28 °C	18 °C, 23 °C, & 28 °C	0.003	0.003	0.007	0.008	0.019	0.024

Figure 2-1: Results and Curve Fit for 18 °C Calibration and 18 °C, 23 °C, and 28 °C Measurements

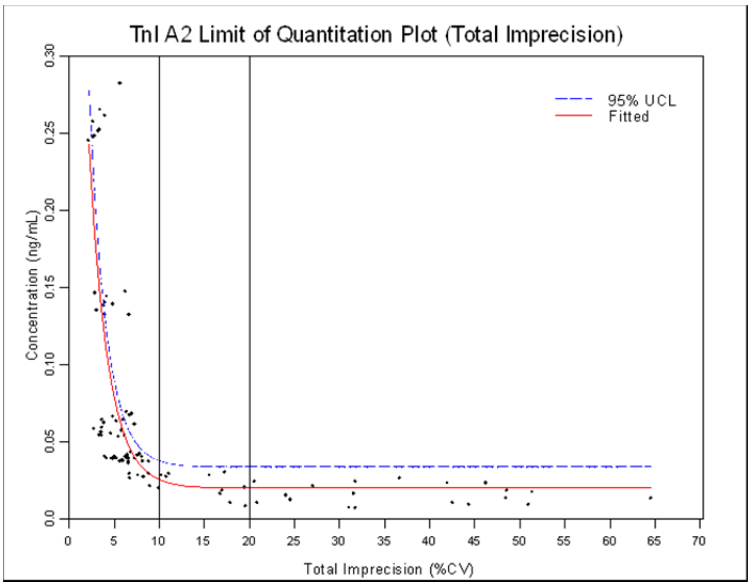


Figure 2-2: Results and Curve Fit for 23 °C Calibration and 18 °C, 23 °C, and 28 °C Measurements

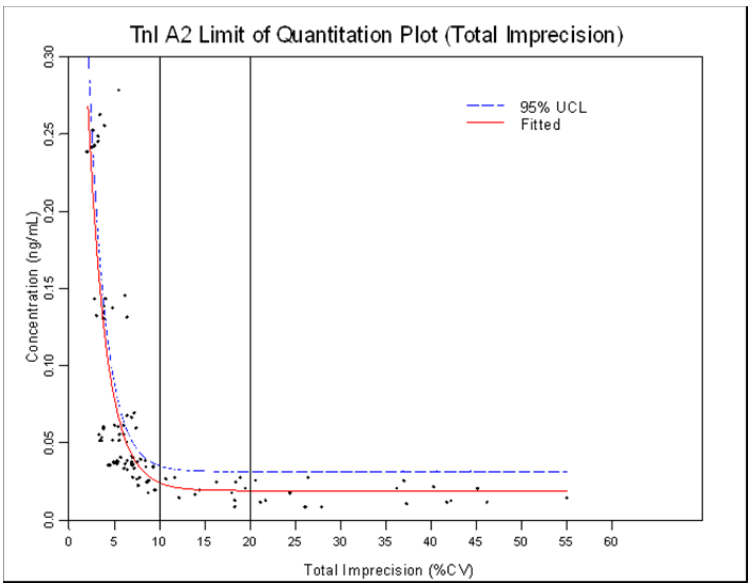
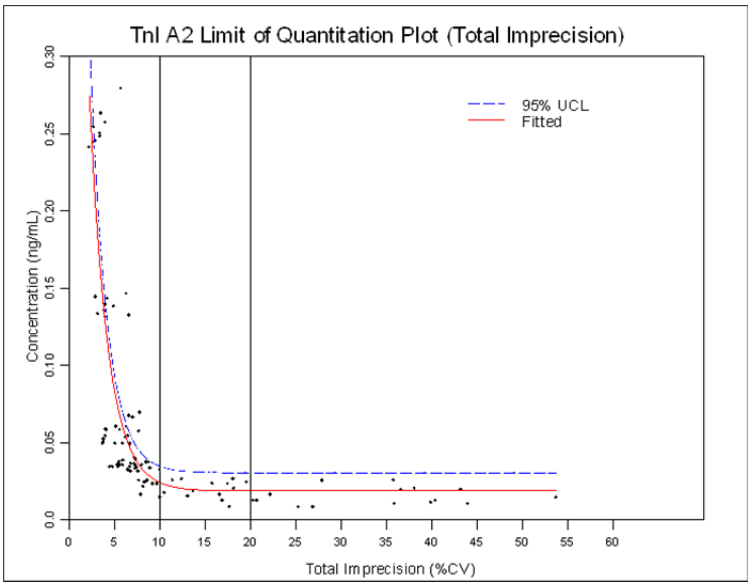


Figure 2-3: Results and Curve Fit for 28 °C Calibration and 18 °C, 23 °C, and 28 °C Measurements



Conclusion: The LoB, LoD, and LoQ for AccuTnI+3 meet all acceptance criteria, regardless of the temperature at which calibration is performed. LoB estimates are all < 0.01 ng/mL; the upper boundaries of the LoD estimates range from 0.008 to 0.010 ng/mL; 20% CV LoQ estimates range from 0.019 to 0.020 ng/mL; and the 10% CV LoQ estimates range from 0.024 to 0.025 ng/mL.

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

All results demonstrate the effectiveness of the thermal algorithm across the operating ambient range of the system and are consistent with those results from previous studies presented in the Submission (k121214).

When evaluated following the recommendations of CLSI EP17-A2, these original studies supported an LoB < 0.01 ng/mL, an LoD of 0.01 ng/mL, and a 10% CV LoQ of 0.03 ng/mL. The 20% CV LoQ achieved in the original studies was 0.01 ng/mL; however, BEC claims a 20% CV LoQ of 0.02 ng/mL, based on the new data presented here.

Lot variability was incorporated into the new study design, as recommended by FDA, and ultimately into the estimates of LoB, LoD, and LoQ. The contribution of reagent pack lot had been evaluated in the original LoQ studies presented in the Submission (k121214), and no significant impact from reagent pack lot was observed. Therefore, we did not specifically evaluate the effect of reagent pack lot on precision estimates for these new studies.

All studies presented to FDA (i.e., both original and new) satisfy the requirements of the CLSI EP17-A2 guideline and demonstrate consistent performance of AccuTnI+3 regardless of calibration temperature or measurement temperature.

Therefore, the AccuTnI+3 labeling contains the following claims:

- ◊ LoB < 0.01 ng/mL, consistent with the upper 97.5th percentile of the measured LoB;
- ◊ LoD = 0.01 ng/mL, consistent with the highest estimate of the "upper-bound" LoD;
- ◊ 20% CV LoQ = 0.02 ng/mL, representing the concentration of troponin I analyte at which AccuTnI+3 achieves 20% CV.
- ◊ 10% CV LoQ = 0.03 ng/mL, representing the concentration of troponin I analyte at which AccuTnI+3 achieves 10% CV.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(2)(b) FDA: (Limit of detection [LoD]): In your response to item 5b, you also reanalyzed samples from the multi-temperature LoD study using calibration curves generated at 18°C and 28°C. As discussed above, this data does not support your LoD claim because those calibrations were not generated at the same time as the samples were measured. Please perform a new LoD study to demonstrate that the LoD is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:

- *Low level patient samples (at least 4) calibrated at 18°C and run at 18°C, 23°C, and 28°C*
- *The same low level patient samples calibrated at 23°C and run at 18°C, 23°C, and 28°C*
- *The same low level patient samples calibrated at 28°C and run at 18°C, 23°C, and 28°C*

We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoD study at each calibration temperature for each lot to confirm the results of your standardized LoD study.

BEC Response to Question 2(b).

BEC has repeated the LoD study as requested by FDA. The protocol for and results of this new study have been provided in our response to Question 2(a) above.

From the new studies, the estimate of LoD is 0.01 ng/mL, which is the same as BEC reported in the Submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(2)(c) FDA: (Limit of quantitation [LoQ]): In your response to item 5c, you reanalyzed the originally-submitted LoQ data to substantiate the LoQ claim. You concluded that your data supports the claim that your device has a 10% CV LoQ of 0.3 ng/mL [sic] and a 20% CV LoQ of 0.02 ng/mL. We do not agree with your conclusion. As discussed above, we cannot use the recalculated data since the calibration curves where not generated at the same time that the samples were measure. Furthermore, you provided data using 7 low level samples on one reagent lot and one instrument which demonstrated that your LoQ is 0.026 with a %CV of 14.2% (data generated at 28°C using instrument 501007). You state that a sample set of 7 is not sufficient to establish an accurate estimate of LoQ. However, each of these 7 samples was measured in 66 replicates. Therefore, it seems that this performance will be experienced by the end user. In order to confirm these results (i.e., LoQ of 0.026 ng/mL with a performance goal of %CV less than 15%), you should provide data from a new LoQ study to demonstrate that the LoQ is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C. We recommend that you provide the following additional data:

- *Low level patient samples (at least 4) calibrated at 18°C and run at 18°C, 23°C, and 28°C*
- *The same low level patient samples calibrated at 23°C and run at 18°C, 23°C, and 28°C*
- *The same low level patient samples calibrated at 28°C and run at 18°C, 23°C, and 28°C*

We recommend that you include at least 2 reagent lots, 3 instruments and testing performed over at least 3 days. You should also follow the recommendations in the EP17-A guideline regarding the number of recommended replicates. Please provide a detailed protocol and the results of your new LoQ study at each calibration temperature for each lot to confirm your LoQ claim.

BEC Response to Question 2(c).

The standardized Limit of Quantitation (LoQ) studies presented in the Submission were designed to be analyzed using CLSI EP17-A2, which is a robust protocol for estimating precision at low concentrations of analyte and utilizes interpolation of data. Under CLSI EP17-A, however, the estimated limit of quantitation (LoQ) is entirely dependent upon the TnI concentrations of the samples used in the studies, rather than upon the number of samples run, the number of replicates run, or the temperature at which the studies were conducted. There were insufficient samples at the critical concentrations to obtain an accurate estimation of LoQ on individual instruments using the EP17-A analysis method. Therefore, the results from multiple instruments were pooled to increase the robustness of the LoQ estimation by EP17-A; this analysis yielded results consistent with our original LoQ estimates and those obtained in our new studies.

BEC has repeated the LoQ study as requested by FDA, following EP17-A2. The protocol for and results of this new study were provided in our response to Question 2(a) above. In addition, we have prepared a summary table containing mean TnI concentrations and % CVs for each sample used in the three temperature-of-calibration experiments. This summary table is located in Appendix 8.

From the new studies, the estimate of 20% CV LoQ is 0.02 ng/mL and 10% CV LoQ is 0.03 ng/mL.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

2(c)(i)	*If you are able to confirm your LoQ claim, you will not be able to report any values under 0.026 ng/mL troponin (or 0.03 ng/mL depending on the decimal points of the reported test results—see question 2cii below) since they are below your LoQ. If this is the case, please reanalyze the data from any study that currently includes data under your LoQ and amend all claims if necessary.*

BEC Response to Question 2(c)(i).

Estimates of LoB, LoD, and LoQ are the outcome of statistical calculations based upon the variability of the measurement procedures.

As described in the CLSI guideline EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*:

- ◊ The limit of detection (LoD) is the "lowest concentration of analyte that can be consistently detected …under routine clinical laboratory conditions…"
- ◊ The limit of quantitation (LoQ) is the "lowest amount of a measurand in a material that can be quantitatively determined with stated accuracy … under stated experimental conditions."

In contrast to LoB and LoD, however, LoQ is based upon acceptance goals with respect to the clinical application of the method.

As indicated above in our response to Question 2(a), for Access AccuTnI+3 on the Access 2 Immunoassay Systems, the LoB and LoD established in our labeling are:

- ◊ LoB < 0.01 ng/mL
- ◊ LoD = 0.01 ng/mL

Our claim for 20% CV LoQ is 0.02 ng/mL, which is the 99th percentile URL for AccuTnI+3. The Third Universal Definition of Myocardial Infarction[†] recommends using cardiac troponin assays having 10% CVs at or below the 99th percentile URL. However, recognizing that not all commercial troponin assays meet the categorization of "highly sensitive," the guideline goes on to say that an assay demonstrating a 20% CV at or below the URL "does not lead to false positive results," indicating that it is acceptable to include the 20% CV LoQ of 0.02 ng/mL within the reportable range of the assay. Furthermore, in the CLSI EP17-A2 guideline, "Results between the LoD and LoQ can be reported, possibly with an associated cautionary notice regarding higher uncertainty in the result." Therefore, the reportable range for AccuTnI+3 is 0.01 ng/mL (LoD) to ~ 100 ng/mL (highest calibrator), and we have added the following statement to our device labeling, in the Limitations of the Procedure section of the Instructions for Use. (See Appendix 3.):

[†]Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. European Heart Journal 2012; 33: 2551–2567. Available online at: www.escardio.org/guidelines.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

◊ "Samples can be accurately measured within the analytical range of the assay (approximately 0.01–100 ng/mL [µg/L]). Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2."

AccuTnI+3 Result (X) on Access 2	Report Result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result <0.01 ng/mL.
0.01 ng/mL (LoD) ≤ **X** < 0.02 ng/mL (20% LoQ)	**X** ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% LoQ)	**X** ng/mL.
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

As noted in CLSI EP17-A2, some automated instruments automatically suppress reporting of very low and negative results. This "censoring of data" gives a truncated results distribution, which prevents the use of parametric data analysis approaches and makes it difficult or impossible for clinical laboratories to conduct testing required by accreditation agencies.

To establish detection limits such as LoB, LoD, and LoQ, all results down to and including zero must be used in the analyses. The replicate requirements in the guidelines for establishing these estimates/claims take into consideration the increased variability at low levels and assure an accurate estimate of the claim. It is not possible to suppress results less than 0.02 ng/mL (20% CV LoQ) or 0.01 ng/mL (LoD) and accurately determine these claims. The testing protocols for the other analytical studies also include sufficient replication to account for increased imprecision at low concentrations. Therefore, all data from these studies are retained in the analyses, and the results of these studies remain valid.

2(c)(ii) It seems that your instrument may report troponin results using two decimal points. If this is the case, and you can verity your current LoQ, you will need to limit your LoQ claim to 0.03 ng/mL with a performance goal of a %CV of 15%.

BEC Response to Question 2(c)(ii).

BEC has the capability to extract data from Access 2 systems in floating point (with all significant digits), and all data analysis (on and off the system) utilizes the full result. The default reporting units for AccuTnI+3 for the end-user are rounded to 2 decimal points (for ng/mL). Therefore, as reported above, the claimed (IFU) LoQ for 20% CV is 0.02 ng/mL, and for 10% CV is 0.03 ng/mL.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 3: Linearity

FDA: In your response to our request for additional information, you provided data from new linearity studies. However, based on the studies you provided, we cannot determine that your device demonstrates acceptable non linearity at the medical decision point at the different temperatures. The reasons are:

(3)(a) FDA: While the lowest sample evaluated was below the LoQ (see item 2c above), the next sample evaluated in the linearity studies contained troponin levels around 10 ng/mL (while the cut-off for the assay is 0.03 ng/mL). Therefore, in order to demonstrate acceptable non-linearity at all temperatures, you will need to provide new studies using patient samples demonstrating the linearity of the device including samples around the cut-off of your device. We recommend that in your new linearity study, you span your claimed range but also include several samples at the lower end of your reportable range (for example a value around your cut-off but above your LoQ and several samples under 1 ng/mL). While we understand that this recommendation deviates from the EP-6 guideline "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach", it is important data that needs to be provided in order to define the linearity of your device including the medical decision point. Please provide a detailed protocol and the results of your new linearity study.

BEC Response to Question 3(a).

Linearity of AccuTnI+3 over the five orders of magnitude of the entire reportable range was demonstrated in our December 14, 2012 response to the First AI Letter. That study included two instruments, two reagent lots, and three temperature conditions, for a total of 12 instrument-reagent-temperature combinations. BEC designed and conducted that linearity study according to CLSI EP6-A.

In Question 3(a) above, FDA has asked BEC to perform a new linearity study, one that would deviate from EP6(-A) in order to include more samples under 1 ng/mL. Assessing linearity over the full assay measuring range, while simultaneously measuring several samples under 1 ng/mL, would require thousand-fold dilutions of the high sample, with the dilution process itself adding additional risk of inaccuracy.

To address FDA's request that we include several samples at the lower end of the reportable range, we designed a new, complementary linearity study to define linearity within the lower two orders of magnitude of the reportable range, again following the EP6-A guideline. BEC's new low-range linearity studies, therefore, augment our earlier set of full-range linearity studies.

The EP6-A guideline recommends using seven to eleven evenly spaced samples to establish linearity across the measuring range. The high sample is blended with the low sample to create the intermediate samples.

To prepare the series of low-end samples on each day of testing, a native lithium heparin plasma sample of approximately 1 ng/mL was blended with a low native lithium heparin plasma sample of ~0.01 ng/mL troponin I to generate five intermediate, evenly spaced concentrations, and is described below in **Table 3-1**.

Study protocol: In these new, low-end studies, the high and low samples were tested neat in replicates of eight while each of the five intermediate mixtures was tested in replicates of four. Three independent studies were performed on one reagent lot and one Access 2 instrument at three temperature conditions including 18 °C, normal laboratory conditions ("NLC"), and 28 °C. Line data for these studies are provided in STATISTICAL DATA/k121214-S001 Line Data.zip, Tab "Q3 Linearity."

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 3-1: Low-Range Linearity Study Sample Preparation

Sample ID	Target Concentration (approximate)	High Sample % Input	Volume(µL) of High Sample used	Low Sample % Input	Volume(µL) of Low Sample used
High	1.00 ng/mL	100%	N/A	0%	0
5	0.80 ng/mL	80%	640	20%	160
4	0.60 ng/mL	60%	480	40%	320
3	0.40 ng/mL	40%	320	60%	480
2	0.20 ng/mL	20%	160	80%	640
1	0.10 ng/mL	10%	80	90%	720
Low	0.01 ng/mL	0%	N/A	100%	N/A

Performance in the new low-end studies was assessed relative to the following acceptance criteria:

◊ The higher order (2nd or 3rd) term of the polynomial fit should be non-significant (p >0.05); or

◊ If the higher order term of the polynomial fit is significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias (maximum deviation from linearity) ≤16% for doses >0.075 ng/mL or ≤0.012 ng/mL for doses ≤0.075 ng/ mL in comparison to the linear regression fit. The tightened acceptance criteria for the low sample are based on the tightened low-dose imprecision criteria, which are described in greater detail below in our response to Question 3(b).

The results are summarized in **Table 3-2** below. Linearity results, including higher order fitted estimates, linearity plots, and difference tables are provided in Appendix 2.

Table 3-2: Summary of Linearity Results at Low TnI Concentrations

Ambient Temperature	Instrument #	Reagent Lot	p-value <0.05?	Maximum Deviation from Linearity	Pass/Fail
18 °C	500537	225962	No	N/A	Pass
NLC	500537	225962	No	N/A	Pass
28 °C	500537	225962	Yes	1%	Pass

Conclusion: In two of the three study conditions, the higher order term of the polynomial fit was non-significant, indicating that the assay is linear. In the third study condition, the third order term is significant, but the maximum deviation from linearity is 1%. Therefore, all studies at all temperatures meet the predefined acceptance criteria for linearity at the critical low end of the AccuTnI+3 measuring range between 0.01 and ~1 ng/mL.

BEC has also prepared a table, similar to the one the Agency provided in the First AI Letter describing FDA's concerns about the apparent temperature dependence of linearity slopes. As seen in **Table 3-3** below, the linear slopes comparing observed and expected results do not indicate residual thermal bias.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 3-3: Comparison of 1st Order Linear Regression Slopes at Low TnI Concentrations

Temp	Reagent	Instrument	Slope	Intercept
18 °C	225962	500537	0.977	0.000
NLC	225962	500537	1.019	0.000
28 °C	225962	500537	0.997	0.000

Conclusion: Taken together, these additional low-range linearity studies and the full-range linearity study included in the December 14, 2012 response to the First AI Letter, demonstrate that AccuTnI+3 is linear across the measuring range of the assay, including the low end of the reportable range between 0.01 and ~1 ng/mL. Both studies also confirm that linearity of the assay is independent of measurement temperature.

(3)(b) FDA: We do not agree with your acceptance criteria for acceptable non-linearity. Specifically, based on your current acceptance criteria for values under 0.105 ng/mL, you will allow 56% deviation from non-linearity [sic] at the medical decision point (please refer to our discussion below in item 8 regarding your acceptance criteria). We also do not concur with deviation from linearity of ≤ 16% for samples > 0.105 ng/mL. Please limit your measuring range to the range with a deviation from non-linearity of around 10% (but not more than 15%). The reason for this recommendation is that deviation from linearity will add to the total error of this device. Therefore, the large deviation currently accepted, may affect the accuracy of this device and affect its safe use.

BEC Response to Question 3(b).

The criteria for acceptable non-linearity of low-level samples have been revised based on the established precision of the device, as noted in our response to Question 8 (Acceptance criteria). Using these tightened criteria, two standard deviations (2 x 0.006 ng/mL) translates to an acceptable deviation-from-linearity specification of ≤ 0.012 ng/mL for samples with troponin I concentrations ≤ 0.075 ng/mL. The use of a standard deviation or absolute concentration difference as criteria for deviation-from-linearity for low concentrations (< 0.075 ng/mL) is appropriate when imprecision is incorporated within the acceptance criteria for linearity. With the new acceptance criteria, the maximum allowed deviation from linearity at the clinical decision point is 0.01 ng/mL. See our response to question 9(a) (Stability), for additional discussion of acceptance criteria near the cutoff.

In the full-range linearity studies described in our response to Question 3(a) above, 90 of the 96 calculated estimates for samples above 0.075 ng/mL (95% of results) had a deviation from linearity less than or equal to 10%, consistent with the specification recommended by the Agency. The maximum deviation from linearity observed in these studies was 14% which is less than the maximum of 15% recommended by the Agency. In the new, low-range linearity studies, the maximum deviation from linearity was 1%.

The combined results of the new low-range linearity studies and the previous full-range linearity studies are in alignment with the performance recommendations provided by FDA, and demonstrate that AccuTnI+3 is linear across the measuring range of the assay and at the medical decision point, and supports the reportable range as stated.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(3)(c) FDA: To also demonstrate that the linearity of your device is not affected by changes in ambient temperature of calibration across the range of 18°C to 28°C, we recommend that you provide data demonstrating acceptable linearity with patient samples run at 18°C, 23°C, and 28°C and calibrated at 18°C, 23°C, and 28°C.

BEC Response to Question 3(c).

To demonstrate that the linearity of Access AccuTnI+3 on the Access 2 Immunoassay Systems is not affected by changes in the ambient temperature of calibration, data from the full-range linearity studies included in the December 14, 2012 response to the First AI Letter were reanalyzed as requested, using alternate calibration curves produced at different temperatures. These curves were generated during those studies at 18 °C, 23 °C, and 28 °C using the same reagent pack lots and instruments. Measurements were calculated from the calibration curves associated with alternate ambient temperatures, and the linearity evaluation was performed again. This cross-temperature evaluation was applied to the full-range linearity study and also to the new low-range linearity study. The slopes of the first order linear regressions, the significance of any higher order polynomial coefficients, and the maximum deviation from linearity observed (if any) are presented in **Table 3-4** and **Table 3-5** below:

Table 3-4: Impact of Calibration and Measurement Temperature on Linearity – Full Range.

Calibration Temperature	Measurement Temperature	Instrument #	Reagent Lot	p-value <0.05?*	Max Deviation from Linearity	Linear Slope
18 °C**	18 °C	500006	225961	Yes	-14%	0.941
18 °C	18 °C	500006	225962	Yes	-12%	0.956
18 °C	18 °C	504050	225961	Yes	-12%	0.950
18 °C	18 °C	504050	225962	Yes	8%	0.968
18 °C	23 °C	500006	225961	Yes	-12%	0.957
18 °C	23 °C	500006	225962	Yes	-12%	0.964
18 °C	23 °C	504050	225961	Yes	10%	0.957
18 °C	23 °C	504050	225962	Yes	-12%	0.955
18 °C	28 °C	500006	225961	Yes	7%	0.967
18 °C	28 °C	500006	225962	Yes	-10%	0.954
18 °C	28 °C	504050	225961	Yes	7%	0.975
18 °C	28 °C	504050	225962	Yes	5%	0.980
23 °C	18 °C	500006	225961	Yes	-13%	0.945
23 °C	18 °C	500006	225962	Yes	-12%	0.954
23 °C	18 °C	504050	225961	Yes	-10%	0.958
23 °C	18 °C	504050	225962	Yes	10%	0.961
23 °C**	23 °C	500006	225961	Yes	-11%	0.961
23 °C	23 °C	500006	225962	Yes	-12%	0.963
23 °C	23 °C	504050	225961	Yes	8%	0.964
23 °C	23 °C	504050	225962	Yes	-14%	0.948
23 °C	28 °C	500006	225961	Yes	6%	0.970
23 °C	28 °C	500006	225962	Yes	-10%	0.953
23 °C	28 °C	504050	225961	Yes	5%	0.982
23 °C	28 °C	504050	225962	Yes	6%	0.975
28 °C	18 °C	500006	225961	Yes	-14%	0.941
28 °C	18 °C	500006	225962	Yes	-10%	0.962
28 °C	18 °C	504050	225961	Yes	-12%	0.951
28 °C	18 °C	504050	225962	Yes	7%	0.970
28 °C	23 °C	500006	225961	Yes	-12%	0.957
28 °C	23 °C	500006	225962	Yes	-10%	0.970
28 °C	23 °C	504050	225961	Yes	10%	0.957
28 °C	23 °C	504050	225962	Yes	-12%	0.958
28 °C**	28 °C	500006	225961	Yes	7%	0.967
28 °C	28 °C	500006	225962	Yes	-8%	0.960
28 °C	28 °C	504050	225961	Yes	7%	0.975
28 °C	28 °C	504050	225962	Yes	4%	0.983

*Quadratic or cubic coefficients

** Results generated from matched calibration/measurement temperature are presented for comparison. The analysis for these instances has been updated from the response to the First AI Letter to align better with EP6-A. While some individual results differ slightly from those originally presented, the maximum deviation from linearity remains the same.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 3-5: Impact of Calibration and Measurement Temperature on Linearity – Low End.

Calibration Temperature	Measurement Temperature	Instrument #	Reagent Lot	p-value <0.05?*	Maximum Deviation from Linearity	Linear Slope
18 °C	23 °C	500537	225962	No	N/A	1.006
18 °C	28 °C	500537	225962	Yes	1%	0.986
23 °C	18 °C	500537	225962	No	N/A	0.989
23 °C	28 °C	500537	225962	No	N/A	0.996
28 °C	18 °C	500537	225962	No	N/A	0.988
28 °C	23 °C	500537	225962	No	N/A	1.020

*Quadratic or cubic coefficients

Conclusion:

In the full-range linearity studies, 95% of the deviation-from-linearity estimates are less than or equal to 10% (297 of 312 estimates) when analyzed across calibration temperatures and measurement temperatures. The maximum deviation from linearity is 14%.

In the low-range linearity studies, the higher order term of the polynomial fit was non- significant in five of the six study conditions, when analyzed across calibration temperatures indicating that the assay is linear. In the sixth study condition, the third order term is significant, but the maximum deviation from linearity is 1%.

Therefore, all studies at all temperatures meet the predefined acceptance criteria for linearity regardless of calibration or measurement temperature, over the full measuring range of the assay.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 4: Precision

FDA: You performed a new precision study using pooled patient samples using 2 reagent lots and 2 instruments at 8 temperatures using calibration curves at 3 temperatures. Please provide the following:

(4)(a) FDA: Please provide overall %CV analysis (i.e., incorporation lot to lot, instrument to instrument and temperature to temperature imprecision) for FDA review. This data should be included in the package insert.

Note to FDA from BEC: This new precision study was performed at 6 temperatures, not 8 temperatures. The study design is described below in our response to Question 4(a).

BEC Response to Question 4(a).

Data from the multi-temperature precision studies that were performed on two Access 2 instruments and two reagent lots using three low-level natural patient sample pools were combined in order to calculate overall imprecision. A total of 48 runs (2 replicates/run) were conducted at 18 °C, 20 °C, 22 °C, 24 °C, 26 °C and 28 °C (8 runs at each temperature) and the results were combined from three different calibration curves, one performed at each of three temperatures (18, 24, and 28 °C) [48 runs x 2 replicates/run x 2 instruments/reagent pack lots x 3 calibration curves = n of 576]. The results are shown below in **Table 4-1**.

Table 4-1: Overall Precision Analysis

			SD (ng/mL)					
Sample	n	Mean Dose (ng/mL)	WithinRun	BetweenRun	BetweenRunTemp	BetweenCalTemp	BetweenIns	Overall*
Pr 001	576	0.04	0.002	0.001	0.001	0.002	0.001	0.003
Pr 002	576	0.43	0.010	0.007	0.016	0.004	0.009	0.022
Pr 003	576	1.01	0.022	0.019	0.028	0.010	0.010	0.043

			%CV					
Sample	n	Mean Dose (ng/mL)	WithinRun	BetweenRun	BetweenRunTemp	BetweenCalTemp	BetweenIns	Overall*
Pr 001	576	0.04	4%	3%	3%	6%	1%	8%
Pr 002	576	0.43	2%	2%	4%	1%	2%	5%
Pr 003	576	1.01	2%	2%	3%	1%	1%	4%

*Overall imprecision includes Within Run, Between Run, Between Run Temperature (BetweenRunTemp), Between Calibration Temperature (BetweenCalTemp), and Between Instrument (BetweenIns) variabilities. Note that in this evaluation, "Between Instrument" variability includes "Between Reagent Lot" variability, since a different reagent lot was run on each instrument.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Overall precision data for the three samples have been included in the IFU (package insert) as shown in **Table 4-2** below:

Table 4-2: Overall Imprecision Table Added to the Revised IFU

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8%
Patient pool 2	0.43	0.022	5%
Patient pool 3	1.01	0.043	4%

Conclusion: The original and revised acceptance criteria for the determination of imprecision were established using EP5-A2 guidelines (i.e., single instrument, single lot). This study meets the revised imprecision criteria of ≤ 8% CV for concentrations > 0.075 ng/mL and ≤ 0.006 SD for concentrations ≤ 0.075 ng/mL even with the added variables of multiple calibrations, temperatures, and instruments. This overall precision analysis has been added to the IFU (See Appendix 3) in the section "Specific Performance Characteristics," subsection "Imprecision." Refer to our response to Question (8) (Acceptance criteria) for additional discussion.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(4)(b) Please provide a detailed protocol for the imprecision data currently provided in the labeling (since it does not match any precision data provided in the 510(k)). Please make sure to provide overall % CV results (incorporating lot to lot, instrument to instrument, temperature to temperature, etc., imprecision) for FDA review and in your package insert.

BEC Response to Question 4(b).

The data in the IFU are the same as the data in the Submission (k121214). The imprecision data provided in the IFU (section "Specific Performance Characteristics," subsection "Imprecision," on page 9) was included in the Submission in Table 37, page 8-23. These data were taken from the 28 °C Temperature Set Point standardized study. Details for this study were provided on page 8-22 of the Submission (Section 8.4.1).

The data provided in the Submission were limited to the data that were necessary to show conformance to the acceptance criteria (rounded to the same number of digits as the acceptance criteria); data provided in the package insert are the same data, and the difference is in presentation only.

We have updated the table that was included in the Submission to include a sample identifier, within-run precision, between-run precision, and total imprecision for all samples and have provided this additional information in **Table 4-3.** The data originally provided in the IFU in the Submission is provided in **Table** 4-4 below for comparison.

Table 4-3: Total Precision, 28 ºC Temperature Set Point, Added to Table 37 from the Submission

Sample	Sample Identified in Table 4-4	n†	Mean Concentration (ng/mL)	Within run (% CV)	Between Run (%CV)	Total SD (ng/mL)	Total %CV
1 (c)	Commercial Control 2	84	1.96	2	5		5
2 (p)	High Patient Pool	84	56.36	5	4		6
3 (s)	Low Patient Pool	84	0.07	5	5	0.0050	7
4 (c)	Commercial Control 1	84	0.91	2	5		5
5 (c)	Commercial Control 3	84	13.97	2	5		5

†Per EP5-A2, a minimum of 40 runs (80 replicates per sample) are required to measure precision.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 4-4: Imprecision Data Provided in original IFU:

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Patient Pool	0.07	5.0	5.0	7.1
Commercial Control 1	0.91	2.0	5.0	5.4
Commercial Control 2	1.96	2.2	4.9	5.3
Commercial Control 3	13.97	2.3	4.7	5.2
High Patient Pool	56.36	5.1	3.9	6.4

Conclusion: The data in the amended IFU, included in Appendix 3 in this Response, have been revised to match the data in **Table 4-3** above.

The precision study described in this section was a standard CLSI EP5-A2 study, based on one instrument and one reagent pack lot. We provide the data from this study design in the IFU to support customer verification activities. Our original study design did not include multiple instruments or reagent lots; therefore, it was not possible to calculate "overall" imprecision. Overall imprecision results based on a separate study requested by the Agency are provided above in our response to Question 4(a) and have been included in the IFU.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 5: Field effectiveness studies

FDA: Please provide the following information regarding your external field effectiveness studies:

(5)(a) FDA: Please provide the thermal bias before and after the application of the thermal algorithm for the external field effectiveness studies.

BEC Response to Question 5(a).

In BEC's December 14, 2012 response to the First AI Letter, we provided additional analysis of the Internal Field Effectiveness study ("Internal FES") data that showed reductions in thermal bias in assay results after application of the thermal algorithm. In the Second AI Letter, the Agency requested a similar assessment of thermal bias in the External Field Effectiveness study ("External FES") data.

During the External FES, ambient laboratory temperatures were not purposefully changed because the evaluations were performed in operational, clinical diagnostic laboratories. As a result, the largest ambient temperature variance observed at any individual site during the External FES was only 4.6 °C and at some sites the temperature variance was less than 2 °C. For this reason, we designed the *Internal* FES study to evaluate the performance of the assay, software, and system by testing specimens under carefully controlled laboratory thermal conditions covering the ambient temperatures from 18 °C to 28 °C, for a range of 10 °C.

When thermal bias was calculated using results from the Internal FES, linear regression was based on results distributed across 10 degrees. When thermal bias is calculated using results from individual sites participating in the External FES, regression analysis is less robust because the results are distributed across only 2-5 degrees at any given site. However, when the results from the five sites are combined, the external sites experienced a collective ambient temperature range of 7.9 °C (from a low of 19.9 °C to a high of 27.8 °C), and the regression analysis is more reliable and robust.

Results are summarized in **Table 5-1** for thermal bias at each site and for all sites combined.

Table 5-1: Before-algorithm to After-algorithm Change in Thermal Bias

			Before Algorithm		After Algorithm	
Site	**Ambient Temp Min and Max during Laboratory Testing (°C)**	**Ambient Lab Temp Range (°C)**	**Change per °C (slope)**	**% Bias Max °C vs. Min °C**	**Change per °C (slope)**	**% Bias Max °C vs. Min °C**
1	22.0 – 23.6	1.6	-1.7	-2.7	0.75	1.2
2	21 – 24	3	-1.99	-6.0	-0.42	-1.3
3	23.9 – 27.8	3.9	-4.41	-17.2	-0.12	-0.5
4	19.9 – 24.5	4.6	-2.47	-11.4	1.33	6.1
5	23.5 – 25.2	1.7	-2.74	-4.7	-0.41	-0.7
Combined	19.9 – 27.8	7.9	-1.38	-10.9	0.21	1.7

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Improvement in thermal bias after application of the thermal algorithm was observed at all sites individually in the External FES, although the extent of the improvement varied by site. Improvement in thermal bias after application of the thermal algorithm was also observed when the data from the sites were combined. In the case of the combined analysis, which more closely reflects the range of ambient temperatures used in the Internal FES, the thermal bias calculated before application of the thermal algorithm was -1.38 which reflects a 1.4% change in reported TnI concentration for every 1 °C change in ambient temperature. After application of the thermal algorithm, the calculated thermal bias was 0.21; this represents less than a 1% change in reported TnI concentration for every 1 °C change in ambient temperature.

Conclusion: These results indicate that the algorithm was effective in reducing the thermal bias in AccuTnI+3 results generated by fielded Access 2 instruments under routine clinical laboratory operating conditions.

Note: Response emailed 4/23/2013 contained Table 5-2 below. In the table below some numbers were not sorted properly as we re-ordered the sites by number. No data are incorrect, but some were just in the wrong order. The Table 5-1 above is correct. There is no change to any of our discussion or our conclusions regarding these tables.

Table 5-2: Before-algorithm to After-algorithm Change in Thermal Bias with incorrect entries

			Before Algorithm		After Algorithm	
Site	Ambient Temp Min and Max during Laboratory Testing (°C)	Ambient Lab Temp Range (°C)	Change per °C (slope)	% Bias Max °C vs. Min °C	Change per °C (slope)	% Bias Max °C vs. Min °C
1	22.0 – 23.6	1.6	-1.7	-2.7	0.75	1.2
2	21 – 24	3	-2.74	-6.0	-0.41	-1.3
3	23.9 – 27.8	3.9	-1.99	-17.2	-0.42	-0.5
4	19.9 – 24.5	4.6	-2.47	-11.4	1.33	6.1
5	23.5 – 25.2	1.7	-4.41	-4.7	-0.12	-0.7
Combined	19.9 – 27.8	7.9	-1.38	10.9	0.21	1.7

(5)(b) FDA: Please confirm that all QC samples used in the external field effectiveness studies also reflect the thermal behavior of natural patient samples. If not, you will need to repeat these studies preferably using unmodified patient samples at relevant troponin concentrations (i.e., around the 0.03 ng/mL cut-off of the device). Please note that FDA still does not agree with your acceptance criteria for concentration > 0.105 ng/mL of ≤ 0.0084 SD since at the medical decision point you are claiming this translates to ± 28% change (refer to item 8 for additional discussion regarding your acceptance criteria). If you need to repeat your studies, please tighten your acceptance criteria based on acceptable clinical performance around the new cut-off of your new device. Please provide a detailed protocol of your new studies, results of your new studies including the recorded ambient temperatures of the laboratories during the testing.

BEC Response to Question 5(b).

The QC samples used in the External FES reflect the thermal behavior of natural patient samples. As noted in the Submission, the External FES included tri-level commercial quality control (QC) samples from two sources (BioRad Laboratories and MORE Diagnostics). The BioRad QC samples are the same samples that were used in the Internal FES, which reflect the thermal behavior of natural patient samples and yield results that are predictive of patient sample results, while the MORE QC samples were included in the Thermal Sensitivity-Robustness study (included in response to question 1(a) above), which demonstrated the effectiveness of the thermal algorithm to appropriately adjust both patient samples and control materials.

Please refer to our responses to Question 8 (Acceptance criteria) for our discussion about our tightened acceptance criteria.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 6: Clinical matrix comparison study

FDA: In order to support that your device can be used using serum samples, you provided Deming regression analysis and Bland-Altman plots from 107 matched serum and plasma samples. You also provided a concordance analysis and ROC characteristic curves for plasma vs. serum samples based on the 0.03 ng/mL cut-off. We have the following concerns with your approach.

(6)(a) FDA: Since your LoQ seems to be 0.03 ng/mL (which is also your medical decision point) you need to exclude samples with values below the LoQ from your Deming regression analysis. This creates a problem for us because we cannot evaluate the quantitative performance of your assay for serum and plasma samples with troponin values below 0.03 ng/mL. Based on the line data from your clinical study, there are 3575 measurements out of a total of 4596 measurements that are below your LoQ (this is about 78% of the results from your clinical study). Therefore, we believe that you need to demonstrate the clinical performance of this device using serum samples. While you provided concordance analysis and ROC analysis comparing plasma and serum samples, it seems that this data is biased since 61% of these samples have a final MI diagnosis compared to around 13% of plasma samples in your clinical study with a final MI diagnosis. Therefore, we still recommend that you evaluate the serum samples from your pivotal clinical study to demonstrate the clinical performance of your device (sensitivity, specificity, negative predictive value and positive predictive value) using serum samples.

BEC Response to Question 6(a).

In our studies, we were able to include results less than 0.03 ng/mL because the protocols contain sufficient replication to account for increased imprecision at low concentrations. For further discussion of reporting results of low concentration, see our response to Question 2(c)(i).

Question 6(a) was discussed with FDA reviewers and managers during a face-to-face discussion with FDA on February 4, 2013 (See Appendix 1.) The Agency agreed to review analytical data in support of matrix equivalence between serum and plasma for AccuTnI+3. Specifically, FDA requested limit of quantitation (LoQ) data using patient serum samples.

BEC has completed new studies as requested by FDA to evaluate limits of quantitation (LoQ) and detection (LoD) of Access AccuTnI+3 on the Access 2 Immunoassay Systems using serum specimens as the test samples, following the CLSI EP17-A2 guidelines. Line data for these studies are provided in STATISTICAL DATA/k121214-S001 Line Data.zip, Tab "Q6 Matrix Comp (Serum LoD-LoQ)." LoD and LoQ were each evaluated at three measurement temperatures and three calibration temperature conditions: 18 °C, 23 °C, and 28 °C. Three days of testing were performed at each temperature condition on two reagent pack lots and three Access 2 instruments. For estimation of LoD, six native serum samples containing low levels of troponin I analyte were measured in two runs of ten replicates each, on each day of testing on each instrument/pack lot combination. For estimation of LoQ, nine native serum samples containing low levels of troponin I analyte were measured in two runs of ten replicates each, for each day of testing on each instrument/pack lot combination. LoD and LoQ were each calculated using measurements from all three temperature conditions and all instrument/pack lot combinations. This study design satisfies the requirements and recommendations of the CLSI EP17-A2 guideline and also allows a multi-temperature evaluation of these statistics. Note that this study design is also in alignment with that requested by FDA in Question 2(b) and 2(c).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

The acceptance criteria for LoD and LoQ were the same for all analyses and identical to those used in the original assessment described in the Submission (k121214):

◊ LoD ≤ 0.030 ng/mL
◊ 20% CV LoQ ≤ 0.03 ng/mL
◊ 10% CV LoQ ≤ 0.06 ng/mL

The results of LoD and LoQ using serum samples as estimated by EP17-A2, and by combining data from multiple temperatures, are shown in **Table 6-1** and in **Figure 6-1**, **Figure 6-2**, and **Figure 6-3** below. Note that these estimates incorporate variability from multiple reagent pack lots, instruments, and temperatures. In addition, we have prepared a summary table containing mean TnI concentrations and % CVs for each serum sample used in the three temperature-of-calibration experiments. This summary table is located in Appendix 9.

Table 6-1: Multi-temperature Serum LoD and LoQ Study using EP17-A2

Calibration Temperature	Measurement Temperatures	Measured LoD (ng/mL)	Upper Bound LoD (ng/mL)	20% CV LoQ (ng/mL)	10% CV LoQ (ng/mL)
18 °C	18, 23, & 28 °C	0.009	0.009	0.020	0.031
23 °C	18, 23, & 28 °C	0.008	0.008	0.018	0.028
28 °C	18, 23, & 28 °C	0.006	0.007	0.015	0.027

Figure 6-1: Serum, 18 °C Calibration, 18 °C, 23 °C, and 28 °C Measurements

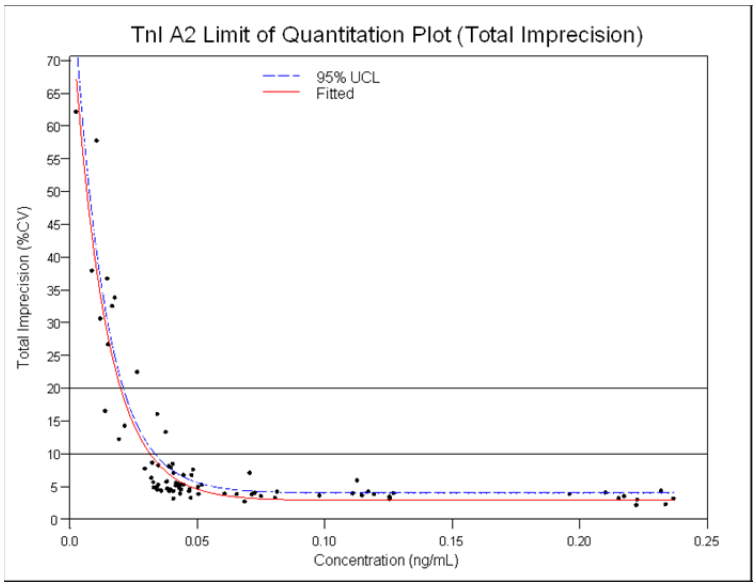


Figure 6-2: Serum, 23 °C Calibration, 18 °C, 23 °C, and 28 °C Measurements

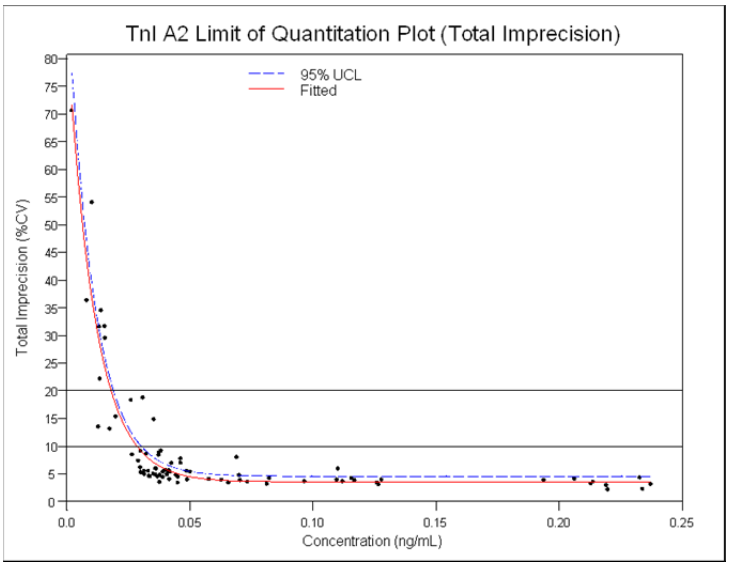
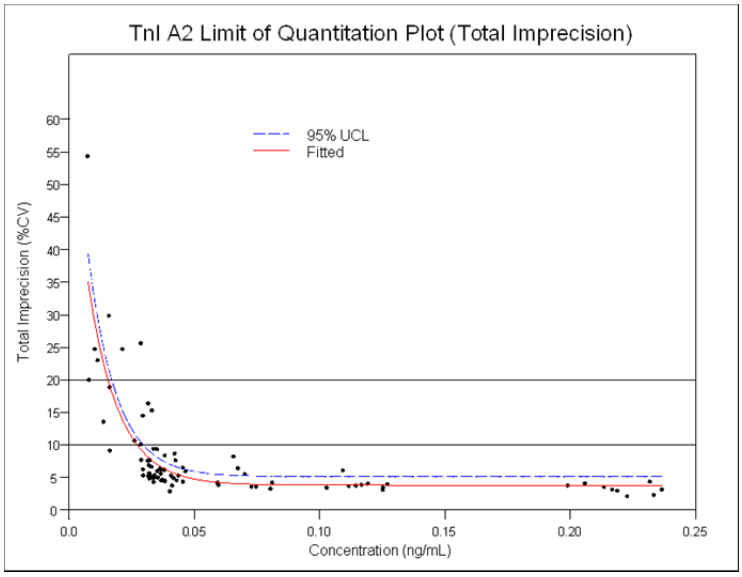


Figure 6-3: Serum, 28 °C Calibration, 18 °C, 23 °C, and 28 °C Measurements



Conclusion: The calculated LoD and LoQ for serum samples across multiple temperatures meet all acceptance criteria regardless of the temperature at which calibration was performed. Furthermore, the LoD and LoQ for the AccuTnI+3 assay on Access 2 for serum samples is consistent with the established LoD and LoQ estimates for lithium heparin plasma samples (Please see our response to Question 2 above).

A side-by-side comparison of the LoQ estimates for plasma and serum is provided in **Table 6-2** below.

Table 6-2: 10% CV LoQ and 20% CV LoQ Comparison for Plasma and Serum

Calibration Temperature	Measurement Temperatures	Plasma 10% CV LoQ (ng/mL)	Serum 10% CV LoQ (ng/mL)	Plasma 20% CV LoQ (ng/mL	Serum 20% CV LoQ (ng/mL)
18 °C	18 °C, 23 °C, & 28 °C	0.025	0.031	0.020	0.020
23 °C	18 °C, 23 °C, & 28 °C	0.024	0.028	0.019	0.018
28 °C	18 °C, 23 °C, & 28 °C	0.024	0.027	0.019	0.015

Conclusion: This serum-plasma LoQ comparison study further demonstrates the equivalence of serum and lithium heparin plasma and specifically demonstrates equivalent performance at the low end of the device measuring range, regardless of calibration temperature or measurement temperature. Therefore, the limits of detection (LoB, LoD, LoQ) as represented in the IFU are appropriate for both sample matrices.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 7: Pivotal Clinical trial

FDA: In response to deficiency 3cii, you stated that adjusting for repeated measures is not appropriate (and for this reason you only use one observation per person per time period) due to the way troponin measures are taken in practice. Please provide a table with all troponin test results from any patient that had multiple draws in a given bin for FDA review.

BEC Response to Question 7.

We have provided the following tables, as requested by FDA, in Appendix 4 and Appendix 5:

- ◊ Linelist AccuTnI Multiple Draws Admission Access 2 Final
- ◊ Linelist AccuTnI Multiple Draws Onset Access 2 Final

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 8: Acceptance criteria

FDA: As we have discussed in several sections above, we do not agree with the acceptance criterion of 0.0084 SD for troponin values under 0.105 ng/mL. While you developed this acceptance criterion based on the decision point of the current assay (i.e., 0.06 ng/mL), since the decision point for the new assay has changed, FDA believes that the acceptance criterion developed for the current assay are not appropriate for the new assay with the new and lower claimed cut-off. For the proposed device with the current cut-off, this criterion seems to translate to ± 28%. Please tighten these criteria to address your new device and your new cut-off. Please amend all necessary claims and update your labeling accordingly.

BEC Response to Question 8.

Precision acceptance criteria for AccuTnI+3 were based on the performance of the currently-marketed AccuTnI device. Based on the pivotal clinical trial outcome, the newly established URL and clinical cutoffs for these assays are substantially lower than those of the currently marketed device. **Table 8-1** below compares the URL, clinical cutoffs, and LoQs of the two devices.

Table 8-1: URL, Cutoff, and LoQ Comparisons of Current and Proposed Devices

	AccuTnI (current device)	AccuTnI+3 (proposed device)
99th Percentile URL	0.04 ng/mL	0.02 ng/mL
Clinical cutoff	0.5 ng/mL	0.03 ng/mL
20% CV LoQ	0.03 ng/mL	0.02 ng/mL
10% CV LoQ	0.06 ng/mL	0.03 ng/mL

Using the outcome of the pivotal clinical trial and the results of the analytical performance testing, we determined that the assay performance of AccuTnI+3 supports tighter precision acceptance criteria. We determined new low-dose precision criteria and updated our design input specifications; these criteria will be used for all future AccuTnI+3 studies and analyses.

All existing data from the verification and validation studies meet the new, tightened criteria. For the proposed device, these criteria translate to ± 20% bias (± 1 SD) at a concentration of 0.03 ng/mL, and align with the LoQ acceptance criteria. These revised criteria more closely align with the established cutoffs of AccuTnI+3 and the performance requirements of troponin assays, as described in the Third Universal Definition of Myocardial Infarction. These new criteria are shown below in **Table 8-2**:

Table 8-2: Comparison of Current Acceptance Criteria to Revised (Tightened Criteria)

	Current Criteria	Revised (Tightened) Criteria
Low-dose Imprecision	SD ≤ 0.0084 ng/mL at TnI concentrations ≤ 0.105 ng/ml	SD ≤ 0.006 ng/mL at TnI concentrations ≤ 0.075 ng/ml
Maximum Bias at 0.03 ng/mL	± 28%	± 20%

Conclusions: The analytical and clinical performance of AccuTnI+3 supports the revised, tightened low-dose acceptance criteria. As requested by FDA, BEC has amended the acceptance criteria and revised all necessary claims and labeling accordingly.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 9: Stability

FDA: We have reviewed the stability data provided in support of your stability claims. We have the following concerns:

(9)(a) FDA: Reagent real time stability and calibrator real time stability:

We are still very concerned that the acceptance criteria for allowable change in your stability studies are too broad for the intended use of this device. Specifically, we are concerned that the Z value uses the observed dose in the calculation and therefore depends on the performance of the device. The acceptance criteria needs to be based on a fixed acceptable change in the performance of the device designed based on the medical needs of the device (e.g., allowable drift of ± 10%). We also disagree with the acceptance criteria that all replicates should be within 3SD (of the expected SD). We are concerned that this is too broad for the intended use of this device. Please narrow your criteria and amend your stability claims. You need to design your acceptance criteria to ensure that a test result is the same at the end of the claimed stability interval compared to the value obtained at baseline. Please provide your reagent and calibrator real time stability data in the same format as you have provided the open pack stability, calibration stability and calibrator open vial stability data to demonstrate acceptable stability in relation to % from baseline (including all individual replicates).

BEC Response to Question 9(a).

This response addresses Question 9 (Stability) in its entirety and includes discussion about reagent pack real-time stability, reagent pack open-pack stability, stored calibration curve stability, calibrator real-time stability, and calibrator open-vial stability. Our response also expresses our tightened acceptance criteria in absolute terms, rather than in terms of "Z," and it shows how our acceptance criteria align with the medical needs of AccuTnI+3, as the Agency has requested.

In **Table 9-1** and

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Table 9-2 below, we compare the revised acceptance criteria for stability to the original criteria for each study type and provide rationale for these changes.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 9-1: In-Use Stability Studies: Acceptance Criteria Comparisons

In-use stability studies: Reagent pack open-pack stability; Stored calibration curve stability; Calibrator open-vial stability	
Original acceptance criteria:	***Revised acceptance criteria:***
Best fit line through all controls and time points at maximum time point (≥ 35 days) must be within ±10.0% of line fit at baseline for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ±125% of the expected SD (0.0084 ng/mL) specification will be applied.	For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 10% (1.25 x 8%) of the y-axis value of the regression line at baseline (time 0).

Statistical rationale for in-use stability acceptance criteria:

The revised specifications are 125% of the tightened low-dose precision specification (SD ≤ 0.006 ng/mL), or 125% of the high-dose imprecision specification (CV ≤ 8%) for each sample. The statistical rationale for setting the specification at 125% of imprecision is described in the footnote below[††].

Clinical rationale for in-use stability acceptance criteria:

Reagent instability may lead to a shift in test results over time. However, for troponin, such shifts are not likely to affect an individual patient sample diagnosis, because serial draws are taken within hours, to detect a rise and/or fall in troponin level. Reagent instability for any assay may also lead to changes in clinical sensitivity and/or specificity over time; however, the following rationale considers why the revised stability acceptance criteria are appropriate for AccuTnI+3 for in-use stability studies:

◊ For low samples (≤ 0.075 ng/mL), the maximum concentration shift allowed under the revised acceptance criteria is ±0.0075 ng/mL (0.01 ng/mL rounded) over the claimed stability time interval. As determined in the pivotal clinical trial, AccuTnI+3 maintains strong clinical performance (sensitivity and specificity) at cutoffs within ± 0.01ng/mL of the recommended ROC-derived cutoff of 0.03 ng/mL. We conclude that clinical utility is maintained throughout the claimed stability interval.

◊ For high samples (> 0.075 ng/mL), the maximum concentration shift allowed under the revised acceptance criteria is 10%. Using a worst case example, a sample with a concentration of 0.08 ng/mL could shift -10% over the stability interval to 0.07 ng/mL. Using the ROC-derived cutoff of 0.03 ng/mL, there would be no change in result classification based on this degree of drift throughout the stability time interval.

[††]A Monte Carlo study, assuming 5% difference is acceptable and an expected imprecision of 8%, provided an additional 5% variability of a regression estimate such that a percent difference specification of ±10% gives 5% type I error. The ratio of specification to imprecision (10%/8% = 125%) was carried over to the difference specification for low-dose samples.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 9-2: 12-Month Real-Time Stability Studies: Acceptance Criteria Comparisons

Real-time stability studies: Reagent pack stability; calibrator stability	
Original acceptance criteria:	***Revised acceptance criteria:***
• All control samples are compared to their stated control values (±2.00 Z from their stated mean) • For each time point tested, individual controls may be greater than ± 2.00 Z from their stated mean as long as that individual control is within ± 1.00Z from baseline • The overall mean Z of control sets cannot be greater than ±1.00 Z from the baseline overall mean Z • All replicates of normal patient samples must be ≤0.04 ng/mL on each instrument at each time point	For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 16% (2 SD) of the y-axis value of the regression line at baseline (time 0). • All replicates of normal samples must be ≤ 0.02 ng/mL on each instrument at each time point.

Statistical rationale for real-time stability acceptance criteria:

◊ The revised specifications are 125% of the tightened low-dose precision specification (SD ≤ 0.006 ng/mL). See the Monte Carlo footnote on the previous page.

◊ For high-dose (> 0.075 ng/mL) samples tested in 12-month stability studies, a ±16% (2 SD) shift from baseline specification has been applied. A specification of ±2 SD is consistent with the methods commonly used in laboratories to establish quality control limits and monitor the performance of an assay.

Clinical rationale for real-time stability acceptance criteria:

Reagent instability may lead to a shift in test results over time. However, for troponin, such shifts are not likely to affect an individual patient sample diagnosis, because serial draws are taken within hours, to detect a rise and/or fall in troponin level. Reagent instability for any assay may also lead to changes in clinical sensitivity and/or specificity over time. The following rationale explains why the current stability specifications are appropriate for AccuTnI+3 for real time stability studies:

◊ The clinical rationale for the specification for low dose samples is the same as for our in-use stability studies.

◊ For high samples (> 0.075 ng/mL), the maximum concentration shift allowed under the revised acceptance criteria is 16%. Using a worst case example, a sample with a concentration of 0.08 ng/mL could shift -16% over the stability interval to 0.07 ng/mL. Using the ROC-derived cutoff of 0.03 ng/mL, there would be no change in result classification based on this degree of drift throughout the stability time interval.

In addition, the specification for normal samples has been revised to reflect AccuTnI+3's 99th percentile URL.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Summary of changes to stability acceptance criteria

The changes described in this response have addressed the concerns of the Agency in the following ways:

◊ Criteria for all low-dose (≤ 0.075 ng/mL) samples have been tightened to align with the imprecision and clinical utility of the assay. (For more information on BEC's revised acceptance criteria, please refer to our response to Question 8 (Acceptance criteria)).
◊ Stability criteria have been developed for individual samples using all replicates, at the recommendation of the Agency and in alignment with CLSI EP25-A.
◊ All individual sample replicates (rather than means) are used to calculate stability profiles.
◊ Because of the revised acceptance criteria and analysis method, "scaling" of low-dose samples is no longer necessary.
◊ Stability criteria for high-dose (> 0.075 ng/mL) samples for short-duration, in-use stability studies have remained at 10%; however, since this specification now applies to individual samples rather than to the mean of all controls, it does represent a tightening of the previous specification.
◊ Criteria for 12-month real-time stability studies (reagent packs and calibrators) are now based on percent or absolute dose shifts rather than "Z values."

Reanalysis of stability data:

For each evaluation of stability (in-use or real-time), a best-fit regression line using all of the individual replicates was constructed through the % difference (high samples) or absolute difference (low samples) from the baseline (y-axis) as a function of time (x-axis). This regression line is then used to calculate the change in dose at the time point of interest. Finally, the result calculated from the regression line is normalized back to the baseline value. For example, results in **Table 9-3** below are calculated as follows:

◊ Low Sample (BRLT1) at 63 days:

- Regression line equation: difference from baseline, ng/mL = (-0.000318) + (0.0000468 x Day)
- Calculation from the equation, at Day 63: (-0.000318) + (0.0000468 x 63) = 0.0026304
- Normalized to baseline: (0.0026304) - (-0.000318) = 0.0029 ng/mL (difference at 63 days)

◊ High Sample (BRLT3) at 63 days:

- Regression line equation: difference from baseline = (100.240663) + (0.03095231 x Day)
- Calculation from the equation, at Day 63: (100.240663) + (0.03095231 x 63) = 102.1906585
- Normalized to baseline: ((102.1906585 / 100.240663) x 100) - 100 = 1.95 (2% change at 63 days)

Linear regression plots for all samples tested are contained in Appendix 6.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 9-3: Calibrator Open-Vial Stability Results on Access 2 (Lot # 119776)

Sample	% Dose Change at 63 Days (Based on Regression Line)	Dose Change at 63 days in ng/mL (Based on Regression Line)	Specification	Pass?
BRLT1		0.0029	+/- 0.0075 ng/mL	Yes
BRLT2	6		+/- 10%	Yes
BRLT3	2		+/- 10%	Yes
MORE3	3		+/- 10%	Yes

Conclusion: Calibrators are stable in an open vial for 60 days.

Table 9-4: Open-Pack and Stored Calibration Curve Stability Results on Access 2

	Stored Curve (Reagent Pack Lot #116678, Cal lot #119776)		*Open Pack (Lot #116678)*			
Sample	% Dose Change at 56 days	Dose Change at 56 days in ng/mL	% Dose Change at 56 days	Dose Change at 56 days in ng/mL	Specification	Pass?
TnI QCPT1		0.0008		0.0035	+/- 0.0075 ng/mL	Yes
MORE2	-7		-3		+/- 10%	Yes
MORE3	-5		-4		+/- 10%	Yes
TnI QCPT2B	-3		2		+/- 10%	Yes

Conclusion: An open reagent pack or a stored calibration curve is stable on Access 2 for 56 days.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 9-5: Reagent Pack Real-Time Stability Results on Access 2

Lot Number	Sample	% Dose Change at 366 Days (Based on Regression Line)	Dose Change at 366 days in ng/mL (Based on Regression Line)	Specification	Pass?
116676	MORE1		0.0044	+/- 0.0075 ng/mL	Yes
116676	MORE2	-13		+/- 16%	Yes
116676	MORE3	-12		+/- 16%	Yes
116676	BRLT1		0.0002	+/- 0.0075 ng/mL	Yes
116676	BRLT2	-12		+/- 16%	Yes
116676	BRLT3	-15		+/- 16%	Yes
116677	MORE1		0.0002	+/- 0.0075 ng/mL	Yes
116677	MORE2	-13		+/- 16%	Yes
116677	MORE3	-9		+/- 16%	Yes
116677	BRLT1		0.0020	+/- 0.0075 ng/mL	Yes
116677	BRLT2	-9		+/- 16%	Yes
116677	BRLT3	-12		+/- 16%	Yes
116678	MORE1		0.0002	+/- 0.0075 ng/mL	Yes
116678	MORE2	-14		+/- 16%	Yes
116678	MORE3	-14		+/- 16%	Yes
116678	BRLT1		-0.0012	+/- 0.0075 ng/mL	Yes
116678	BRLT2	-14		+/- 16%	Yes
116678	BRLT3	-16		+/- 16%	Yes

Conclusion: All three reagent pack lots meet stability specifications, supporting a shelf life of 365 days (12 months).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 9-6: Calibrator Real-Time Stability Results on Access 2

Lot Number	Sample	% Dose Change at 366 Days (Based on Regression Line)	Dose Change at 366 days in ng/mL (Based on Regression Line)	Specification	Pass?
117302	MORE1		-0.0023	+/- 0.0075 ng/mL	Yes
117302	MORE2	-2		+/- 16%	Yes
117302	MORE3	3		+/- 16%	Yes
117302	BRLT1		-0.0006	+/- 0.0075 ng/mL	Yes
117302	BRLT2	-5		+/- 16%	Yes
117302	BRLT3	-9		+/- 16%	Yes
117455	MORE1		0.0007	+/- 0.0075 ng/mL	Yes
117455	MORE2	6		+/- 16%	Yes
117455	MORE3	7		+/- 16%	Yes
117455	BRLT1		0.0015	+/- 0.0075 ng/mL	Yes
117455	BRLT2	-1		+/- 16%	Yes
117455	BRLT3	-5		+/- 16%	Yes
119776	MORE1		0.0012	+/- 0.0075 ng/mL	Yes
119776	MORE2	7		+/- 16%	Yes
119776	MORE3	7		+/- 16%	Yes
119776	BRLT1		0.0015	+/- 0.0075 ng/mL	Yes
119776	BRLT2	2		+/- 16%	Yes
119776	BRLT3	1		+/- 16%	Yes

Conclusion: All three calibrator lots meet stability specifications, supporting a shelf life of 365 days (12 months).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(9)(b) FDA: Reagent open pack, calibration stability and open vial calibrator stability:

While it seems that the majority of the replicates in your reagent open pack, calibration stability and calibrator open vial stability studies demonstrate acceptable drift (generally within ± 10% from baseline), we are concerned that the acceptance criteria are too broad for the intent of this testing. As discussed above for reagent real time stability, we recommend that you narrow your criterion (e.g., allowable drift of ± 10%) and amend your claims if necessary. You need to design your acceptance criteria to ensure that a test result is the same at the end of the claimed stability interval compared to a value at baseline.

BEC Response to Question 9(b).

Please see our response to all of Question 9 above, under 9(a).

Question 10: Calibrators

FDA: You provided additional information about the value assignment process for the calibrators. You state that the acceptance criteria for value assignment is SD ≤ 0.0084 for S1 (the 0 calibrator) and 8% for S2 to S6. You provided a table with data for 3 calibrator lots. You state that doses generated from pre-specified RLU's that are < 0.04 ng/mL are not used for evaluation. Please explain why you do not evaluate doses less than 0.04 ng/mL (which is above your medical decision cut-off). It seems that doses above your LoQ need to be evaluated. You list the following reference doses (lot 117302 as an example) in table I; 0.044, 0.626, 0.13, 0.21, 0.28, 0.31, 0.66, 1.00, 1.34, 1.69, 2.37, 3.05, 3.73, 4.76, 6.14, 7.54, 10.39, 14.05, 17.84, 21.77, 25.85, 30.10, 39.16 and 65.76. It is not clear what these results are (i.e., what was measured, calibrators, quality control samples, patient samples, etc.). Please explain what these results are and how they are substantiating the assigned value of your kit calibrators. Please provide more information about the acceptance criteria for calibrator value assignment. For example, which assay results need to be within 0.0084SD and which results need to be within 8%. Please refer to item 8 for discussion regarding our concern with your acceptance criteria. We do not believe that an allowable drift of 28% around the medical decision point of this assay is appropriate for its calibrators. Also, you state that dose values for commercial calibrators must fall within quality control ranges. Please specify these ranges for each calibrator and discuss why you believe they are appropriate for the intended use of this device. Please specify how your procedure controls drift in the assigned value of the kit calibrators in subsequent calibrator lots.

BEC Response to Question 10.

Please note: In this response, BEC uses the term "dose" or "dose response" to describe the Access 2 instruments' computed output in concentration units of ng/mL. The system calculates troponin doses from the amount of light emitted by the chemiluminescent reaction, which, in turn, is detected by the instrument and measured in relative light units, or RLUs.

In our initial studies, we did not evaluate doses less than 0.04 ng/mL because the cutoff for evaluation had been based on the 99th percentile URL of the currently-marketed AccuTnI assay. BEC has since revised the cutoff for evaluation to 0.02 ng/mL, based on the 99th percentile URL established during the pivotal clinical trial for AccuTnI+3, and has re-evaluated the data generated previously against the new 99th percentile URL of 0.02 ng/mL.

In addition, and consistent with our response to Question 8 (Acceptance criteria), BEC has revised its acceptance criteria for verifying calibrator value assignments. We have provided new data tables below, clarifying which assay results are subject to an 8% difference acceptance criterion and which ones must meet a specified difference criterion in absolute units (0.006 ng/mL).

In the section below, we have included a more complete description of BEC's calibrator value verification process using a set of primary reference calibrators. The three tables (three calibrator lots) following that description below more clearly describe our verification results and how those results substantiate the assigned value of the kit calibrators. Finally, BEC confirms new calibrator performance by testing independent, external quality control samples having labeled TnI value ranges. *Please note that while each individual AccuTnI+3 calibrator (S1, S2, etc.) is manufactured—and verified—to be within a specified range of TnI concentrations, final acceptance criteria for commercial calibrators are based on the performance of the calibrator set as a whole and not on TnI concentrations of individual calibrators.*

To clarify the statement in the Calibrator 510(k), "Dose values for commercial calibrators must fall within quality control ranges," BEC's calibrator confirmation process is better described as follows: Using a

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calibration curve generated by the newly value-assigned commercial calibrators, Quality Control samples are tested and must meet the ranges established for those controls.

For more information about the preparation and value assignment of AccuTnI+3 calibrators, please refer to the abbreviated calibrator 510(k) in Appendix 11 of our December 14, 2012 response to the First AI Letter.

Verification of assigned calibrator values:

The Access 2 instrument measures the light output ("relative light units," or "RLUs") of the chemiluminescent reaction of an unknown patient sample. The instrument then calculates the TnI concentration (referred to as the "dose") of the sample by comparing its RLUs to a standard curve ("calibration curve") generated from AccuTnI+3 calibrators with assigned TnI concentrations. Under ordinary operating conditions, RLUs are generated by testing samples on the instrument. However, BEC can also calculate simulated dose results from a set of "pre-specified RLUs." The use of pre-specified RLUs offers the advantage of being able to evaluate discrete RLU values across the full range of the calibration curve.

To verify calibrator value assignments of a new lot of calibrators, BEC generates two different sets of calibration curves. One set of calibration curves are reference (REF) curves, generated from replicates of the primary reference calibrators. The second set of calibration curves (TEST) come from replicates of the newly manufactured commercial calibrators. The resulting calibration curves are used to generate dose values from a set of pre-specified RLUs spanning the reportable range of the assay.

Pre-specified RLUs are converted to TnI doses using both sets of calibration curves, and the differences in dose between the REF curves and the TEST curves are statistically compared. For doses ≤ 0.075 ng/mL, the lower and upper 95% confidence limits around the mean difference between TEST and REF results must be between -0.006 ng/mL and +0.006 ng/mL. For doses > 0.075 ng/mL, the lower and upper 95% confidence limits around the mean difference between TEST and REF results must be within ±8% of the REF result. In the tables below, the ± 8% specification is converted to SD.

This verification process uses primary reference calibrators to control drift in the value assignment of every lot of new commercial calibrators. Each new lot of commercial calibrators must meet the same criteria with respect to the primary reference calibration curve.

In **Table 10-1**, **Table 10-2**, and **Table 10-3** below, Mean REF Dose and Mean TEST Dose are the results generated for each pre-specified RLU from the REF calibration curve and the TEST calibration curve, respectively. *Please note: Rows for very low or very high pre-specified RLUs are grayed out if any calculated dose is lower than or higher than the reportable range of AccuTnI+3.*

Table 10-1: Verification of Value Assignments - Calibrator Lot 117302

Pre-specified RLU	Mean REF Dose (ng/mL)	Mean TEST Dose (ng/mL)	Mean TEST Dose *minus* Mean REF Dose	Lower 95% CI	Upper 95% CI	Specification (±)	Results
10000							
15000							
20000	0.0259	0.0248	-0.0011	-0.0024	0.0001	0.0060	PASS
25000	0.0444	0.0430	-0.0014	-0.0025	-0.0002	0.0060	PASS
30000	0.0626	0.0610	-0.0016	-0.0026	-0.0005	0.0060	PASS
50000	0.1345	0.1324	-0.0020	-0.0030	-0.0010	0.0108	PASS
70000	0.2054	0.2031	-0.0023	-0.0035	-0.0011	0.0164	PASS
90000	0.2758	0.2734	-0.0024	-0.0040	-0.0008	0.0221	PASS
100000	0.3109	0.3084	-0.0024	-0.0043	-0.0006	0.0249	PASS
200000	0.6580	0.6563	-0.0017	-0.0058	0.0025	0.0526	PASS
300000	1.0017	1.0019	0.0002	-0.0062	0.0065	0.0801	PASS
400000	1.3438	1.3465	0.0026	-0.0059	0.0112	0.1075	PASS
500000	1.6851	1.6907	0.0055	-0.0051	0.0162	0.1348	PASS
700000	2.3669	2.3792	0.0124	-0.0022	0.0270	0.1893	PASS
900000	3.0489	3.0692	0.0202	0.0019	0.0386	0.2439	PASS
1100000	3.7326	3.7614	0.0288	0.0070	0.0506	0.2986	PASS
1400000	4.7623	4.8050	0.0427	0.0160	0.0694	0.3810	PASS
1800000	6.1458	6.2085	0.0627	0.0302	0.0951	0.4917	PASS
2200000	7.5434	7.6273	0.0839	0.0463	0.1215	0.6035	PASS
3000000	10.3877	10.5166	0.1289	0.0831	0.1748	0.8310	PASS
4000000	14.0469	14.2353	0.1883	0.1349	0.2418	1.1238	PASS
5000000	17.8353	18.0848	0.2496	0.1895	0.3096	1.4268	PASS
6000000	21.7654	22.0767	0.3113	0.2421	0.3805	1.7412	PASS
7000000	25.8497	26.2223	0.3725	0.2868	0.4583	2.0680	PASS
8000000	30.1007	30.5330	0.4323	0.3188	0.5458	2.4081	PASS
10000000	39.1558	39.6992	0.5434	0.3336	0.7533	3.1325	PASS
15000000	65.7576	66.4734	0.7158	-0.0344	1.4659	5.2606	PASS
20000000							

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 10-2: Verification of Value Assignments - Calibrator Lot 117455

Pre-specified RLU	Mean REF Dose (ng/mL)	Mean TEST Dose (ng/mL)	Mean TEST Dose *minus* Mean REF Dose	Lower 95% CI	Upper 95% CI	Specification (±)	Results
10000							
15000							
20000							
25000	0.0412	0.0431	0.0019	-0.0019	0.0058	0.0060	PASS
30000	0.0595	0.0612	0.0017	-0.0016	0.0050	0.0060	PASS
50000	0.1316	0.1325	0.0008	-0.0012	0.0029	0.0105	PASS
70000	0.2030	0.2030	0.0001	-0.0018	0.0019	0.0162	PASS
90000	0.2738	0.2731	-0.0006	-0.0031	0.0018	0.0219	PASS
100000	0.3090	0.3080	-0.0010	-0.0038	0.0019	0.0247	PASS
200000	0.6587	0.6545	-0.0042	-0.0109	0.0025	0.0527	PASS
300000	1.0055	0.9984	-0.0071	-0.0166	0.0025	0.0804	PASS
400000	1.3510	1.3412	-0.0098	-0.0216	0.0021	0.1081	PASS
500000	1.6958	1.6835	-0.0123	-0.0261	0.0014	0.1357	PASS
700000	2.3850	2.3679	-0.0171	-0.0342	-0.0001	0.1908	PASS
900000	3.0751	3.0535	-0.0216	-0.0418	-0.0014	0.2460	PASS
1100000	3.7671	3.7413	-0.0258	-0.0495	-0.0020	0.3014	PASS
1400000	4.8098	4.7783	-0.0315	-0.0612	-0.0017	0.3848	PASS
1800000	6.2113	6.1730	-0.0383	-0.0778	0.0012	0.4969	PASS
2200000	7.6275	7.5833	-0.0442	-0.0950	0.0067	0.6102	PASS
3000000	10.5100	10.4568	-0.0532	-0.1303	0.0238	0.8408	PASS
4000000	14.2183	14.1587	-0.0596	-0.1734	0.0543	1.1375	PASS
5000000	18.0560	17.9960	-0.0600	-0.2131	0.0932	1.4445	PASS
6000000	22.0352	21.9812	-0.0540	-0.2476	0.1396	1.7628	PASS
7000000	26.1676	26.1267	-0.0409	-0.2758	0.1939	2.0934	PASS
8000000	30.4650	30.4450	-0.0200	-0.2967	0.2567	2.4372	PASS
10000000	39.6052	39.6545	0.0492	-0.3160	0.4145	3.1684	PASS
15000000	66.3312	66.7779	0.4467	-0.2757	1.1691	5.3065	PASS
20000000							

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 10-3: Verification of Value Assignments - Calibrator Lot 119776

Pre-specified RLU	Mean REF Dose (ng/mL)	Mean TEST Dose (ng/mL)	Mean TEST Dose *minus* Mean REF Dose	Lower 95% CI	Upper 95% CI	Specification (±)	Results
10000							
15000							
20000	0.0334	0.0350	0.0017	-0.0015	0.0048	0.0060	PASS
25000	0.0548	0.0572	0.0024	-0.0008	0.0055	0.0060	PASS
30000	0.0760	0.0790	0.0030	-0.0002	0.0061	0.0061	PASS
50000	0.1591	0.1642	0.0051	0.0017	0.0084	0.0127	PASS
70000	0.2409	0.2477	0.0068	0.0031	0.0105	0.0193	PASS
90000	0.3218	0.3301	0.0083	0.0042	0.0124	0.0257	PASS
100000	0.3620	0.3710	0.0090	0.0047	0.0133	0.0290	PASS
200000	0.7592	0.7735	0.0143	0.0080	0.0206	0.0607	PASS
300000	1.1510	1.1689	0.0179	0.0092	0.0266	0.0921	PASS
400000	1.5402	1.5606	0.0204	0.0088	0.0319	0.1232	PASS
500000	1.9278	1.9500	0.0222	0.0073	0.0370	0.1542	PASS
700000	2.7008	2.7248	0.0240	0.0014	0.0465	0.2161	PASS
900000	3.4732	3.4972	0.0241	-0.0072	0.0553	0.2779	PASS
1100000	4.2465	4.2693	0.0229	-0.0177	0.0635	0.3397	PASS
1400000	5.4105	5.4296	0.0191	-0.0365	0.0747	0.4328	PASS
1800000	6.9734	6.9846	0.0112	-0.0655	0.0878	0.5579	PASS
2200000	8.5520	8.5525	0.0005	-0.0979	0.0989	0.6842	PASS
3000000	11.7655	11.7379	-0.0276	-0.1702	0.1150	0.9412	PASS
4000000	15.9047	15.8316	-0.0731	-0.2699	0.1237	1.2724	PASS
5000000	20.1986	20.0701	-0.1285	-0.3763	0.1193	1.6159	PASS
6000000	24.6649	24.4719	-0.1930	-0.4868	0.1008	1.9732	PASS
7000000	29.3204	29.0542	-0.2662	-0.5999	0.0674	2.3456	PASS
8000000	34.1824	33.8343	-0.3481	-0.7149	0.0186	2.7346	PASS
10000000	44.6000	44.0612	-0.5388	-0.9537	-0.1240	3.5680	PASS
15000000	75.7388	74.5413	-1.1975	-1.9229	-0.4720	6.0591	PASS
20000000							

Question 11: Labeling

FDA: Please amend your claims based on the recommendation above.

BEC Response to Question 11.

BEC has made the following additions and/or changes to our Instructions for Use (IFU) (See Appendix 3):

- ◊ As requested in Question 4(b) (Precision), we have included our overall precision analysis in the product labeling (IFU).
- ◊ We have amended our performance claims in the IFU as requested in Question 8 (Acceptance criteria). Precision and linearity claims for AccuTnI+3 have been updated.
- ◊ Based on the outcome of the limit of detection studies described in our response to Question 2(a), LoB, LoD, LoQ sections of the IFU have been updated.
- ◊ As described in our response to Question 2(c)(i) (Limits of detection), recommendations for reporting results above and below the analytical measuring range of the assay have been added to the labeling. Please refer to the "Limitations of the Procedure" section of the IFU, Item 3.
- ◊ BEC has added the following statement to the "Limitations of the Procedure" section of the IFU, Item 6, regarding different types of troponin antigens. "The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g., recombinant antigens) may behave differently."

(11)(a) FDA: Please include the sensitivity, specificity, positive predictive value and negative predictive value performance of your device for the ≥ 6-9 hour time interval.

BEC Response to Question 11(a).

The sensitivity, specificity, positive predictive value and negative predictive value for the ≥ 6-9 hour time interval have been included in the IFU, as requested.

(11)(b) FDA: Since your corrective algorithm was designed to reduce the thermal sensitivity from around 3.5% to <1% per degree, we recommend that you include this information in the package insert.

BEC Response to Question 11(b).

BEC has added the following limitation to the IFU to augment the existing statement regarding the operating temperature range for AccuTnI+3. Please refer to the "Limitations of the Procedure" section of the IFU, Item 2.

"This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F)."

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Question 12: 510(k) Summary

FDA: Please submit a new intended use form and 510(k) summary with your response (if necessary).

BEC Response to Question 12.

The new Indications for Use form, which uses the latest revision of the approved Indications for Use template, and 510(k) Summary are provided in Appendix 7.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 1: FDA face-to face meeting minutes from February 4, 2013, referenced in the response to Question 1(b).

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RECORD OF MEETING

Product Name: Access AccuTnI on the Access 2 Immunoassay Systems (k121214)
Sponsor: Beckman Coulter, Inc.
Meeting Date/Time: February 4, 2013 at 11:00A.M.
Meeting Format: Face to face meeting
Meeting Recorder: Paula Caposino

FDA Attendees:
Paula Caposino, Lead Reviewer, Office Of In Vitro Diagnostics And Radiological Health (OIR), Division Of Chemistry And Toxicology Devices (DCTD)
Ileana Elder, Compliance Team Leader, OIR/DCTD
Ruth Chesler, Cardio-Renal Branch Chief, OIR/DCTD
Carol Benson, Deputy Division Director, OIR/DCTD
Alberto Gutierrez, Office Director, OIR

Danaher Corporation Attendee:
Jonathan Graham, Senior Vice President and General Counsel

Beckman Coulter, Inc. Attendees:
Clair O'Donovan, Senior Vice President Quality and Regulatory Affairs
Scott Cundy, Vice President Quality and Regulatory Affairs
Kurt Bray, Principal Clinical Studies
Corey Carlson, Manager of Reagent Development

Subject: Beckman Coulter, Inc. requested a meeting to discuss the matrix comparison study deficiency and the temperature concordance study deficiency identified during the review k121214-S001 (for the Access AccuTnI on the Access 2 Immunoassay System).

Items Discussed:

1. Matrix Comparison Study: The agency agreed to review analytical data in support of matrix equivalency between serum and plasma for the proposed device as a mean to resolve the matrix comparison study deficiency identified in FDA's January 8, 2013 letter requesting additional information (item 6). Specifically, the agency requested limit of quantitation (LoQ) data using serum patient samples spanning the operating temperature of the device to demonstrate that the LoQ of the device using serum samples is equivalent to the LoQ of the device using lithium heparin plasma samples. For the new serum LoQ studies, the agency recommended that the sponsor follow the recommendations in FDA's letter requesting additional information (item 2c). The agency also requested that the sponsor provide linearity data using serum samples, if this data is available.

2. Temperature concordance study: The sponsor has not been able to determine root cause for the temperature concordance study provided in the original 510(k) that did not demonstrate that the corrective algorithm resolved the temperature sensitivity issue of the device. During the meeting, the sponsor expressed concern that without definitive root cause the agency will not consider the deficiency resolved. FDA stated that the sponsor needs to resolve the

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deficiency. If root cause is not definitively determined, the agency recommended that the sponsor propose an approach to make sure that the corrective algorithm is safe and effective and if it fails in the intended use setting, that the sponsor has a mechanism in place to ensure patient safety.

3. DxI Extension: The agency agreed to grant the sponsor an additional 180 day extension for the Access AccuTnI on the UniCel DxI Immunoassay Systems (k121790). The current extension expires on February 19, 2013. FDA agreed to grant an extension.

FDA thanked the sponsor for travelling to FDA's campus to discuss the deficiencies. The meeting concluded at 12:00 P.M.

Reviewer Name and Signature:

Paula V. Caposino, Ph.D.
FDA/CDRH/OIR/DCTD

Questions? Contact FDA/CDRH/OCE/DDM CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Appendix 2: Linearity results, including higher order fitted estimates, linearity plots, and difference tables referenced in the response to Question 3(a).

Table A2-1: Reagent Pack 225962, Instrument 500537, 18°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0002	0.5405
	X	0.9770	0.0000
2nd	Intercept	0.0005	0.2810
	X	0.9547	0.0000
	X^2	0.0415	0.2989
3rd	Intercept	0.0005	0.5154
	X	0.9605	0.0002
	X^2	0.0093	0.9613
	X^3	0.0293	0.8633

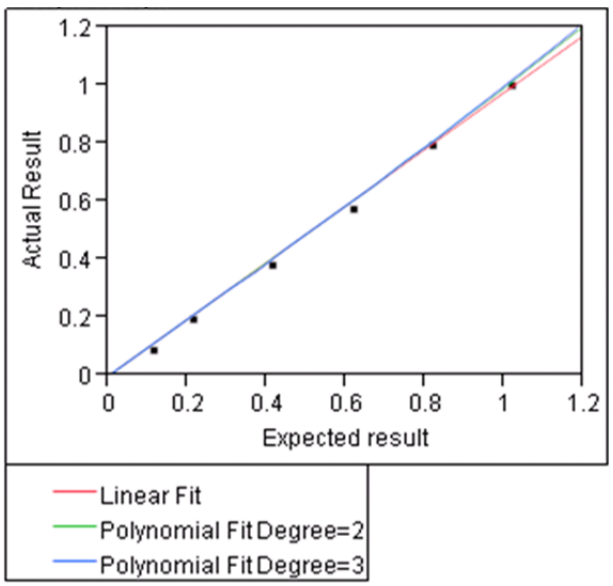

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Table A2-2: Reagent Pack 225962, Instrument 500537, NLC

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	-0.0002	0.4140
	X	1.0191	0.0000
2nd	Intercept	-0.0003	0.3637
	X	1.0280	0.0000
	X^2	-0.0119	0.5812
3rd	Intercept	0.0000	0.8930
	X	0.9955	0.0000
	X^2	0.1158	0.1894
	X^3	-0.0828	0.1514

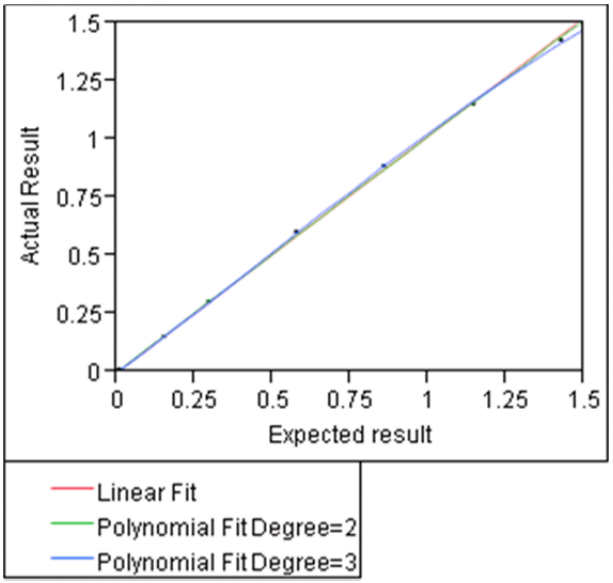

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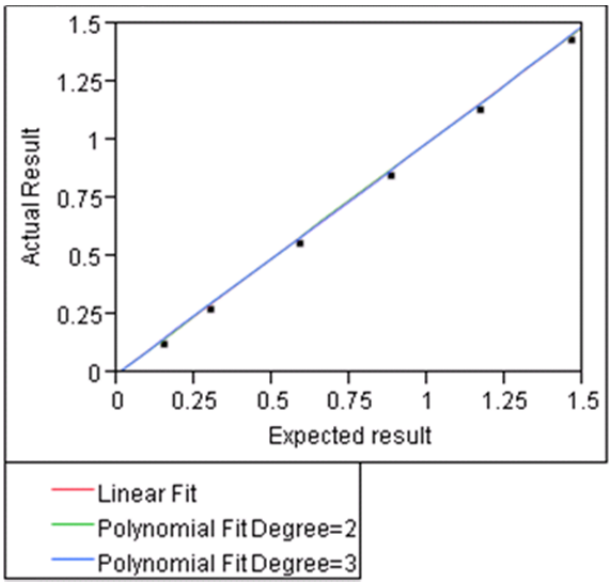
Table A2-3: Reagent Pack 225962, Instrument 500537, 28°C

Poly Order	Coefficient Term	Parameter Estimate	p-value
1st	Intercept	0.0000	0.6056
	X	0.9969	0.0000
2nd	Intercept	0.0000	0.9614
	X	1.0005	0.0000
	X^2	-0.0048	0.4018
3rd	Intercept	-0.0001	0.1220
	X	1.0108	0.0000
	X^2	-0.0442	0.0353
	X^3	0.0249	0.0442



Sample	Expected (ng/mL)	Linear	Cubic	Deviation from Linearity (ng/mL)	% Deviation from Linearity
Sample 1 Low	0.0058	0.0059	0.0059	0.0000	
Sample 2	0.1514	0.1509	0.1521		1%
Sample 3	0.2969	0.2960	0.2969		0%
Sample 4	0.5879	0.5861	0.5842		0%
Sample 5	0.8790	0.8763	0.8713		-1%
Sample 6	1.1700	1.1664	1.1620		0%
Sample 7 High	1.4611	1.4565	1.4599		0%

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Appendix 3: Instructions for Use (IFU)

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143 FOR USE ON ACCESS 2 SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay Systems to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG;

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- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 systems)

Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination.

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Store and dispose of these materials and their containers in accordance with local regulations and guidelines.

- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
107	0.01–20	0.00 (0.00–0.00)	1.00 (0.98–1.00)	1.00
104	0.01–5	0.00 (0.00–0.00)	1.00 (1.00–1.00)	1.00

   Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

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Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

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Limitations of the Procedure

1. This product is for use on Access 2 systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. Samples can be accurately measured within the analytical range of the assay (approximately 0.01–100 ng/mL [µg/L]). Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2:[35]

AccuTnI+3 Result (X) on Access 2	Report result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result <0.01 ng/mL
0.01 ng/mL (LoD) ≤ **X** < 0.02 ng/mL (20% LoQ)	**X** ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% LoQ)	**X** ng/mL
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[21,22] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[23,24] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[25] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

Expected Values

Apparently Healthy Adults

Each laboratory should establish its own reference ranges to assure proper representation of specific populations and sample types, and to reflect current practice at their institutions.

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary

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angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

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Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[26] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94– 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated

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cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility. Each facility should evaluate prevalence at their institution and adjust PPV and NPV accordingly.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility. Each facility should determine prevalence at their institution and adjust PPV and NPV accordingly.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for

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myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 system. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of < 16% for samples > 0.075 ng/mL (µg/L), and < 0.012 ng/mL (µg/L) for samples ≤ 0.075 ng/mL (µg/L).

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (µg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (µg/L) at concentrations ≤ 0.075 ng/mL (µg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a minimum of 10 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8%
Patient pool 2	0.43	0.022	5%
Patient pool 3	1.01	0.043	4%

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run on five Access 2 systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL

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Substance	Highest Concentration Added
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	48.75 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Ibuprofen	50 mg/dL
Low MW Heparin	71 µg/mL
Methyldopa	2.5 mg/dL
Nifedipine	6 µg/dL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	200 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

Limit of Blank

The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[35]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[35]

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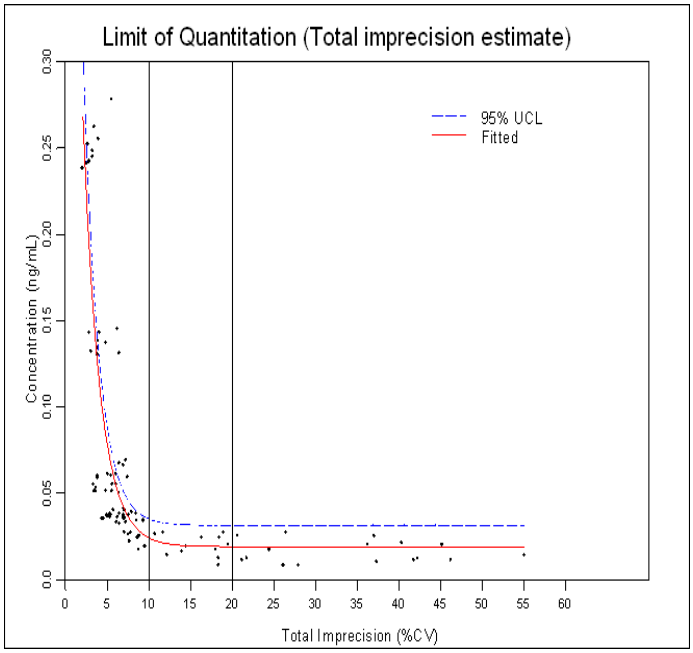
Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.03 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[35] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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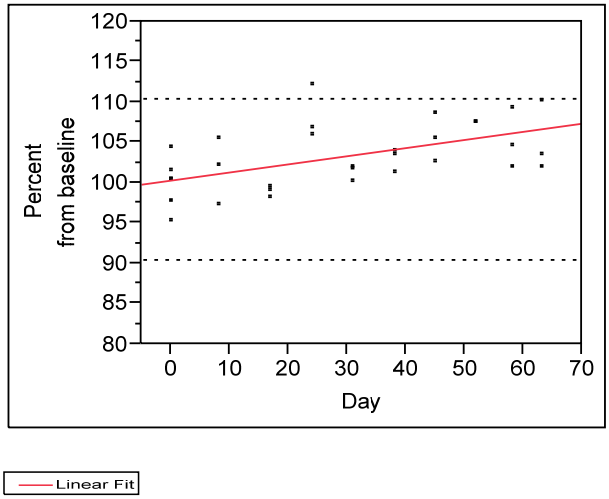
Figure A6- 2: Access 2 Calibrator Open-vial Bivariate Fit of Percent from Baseline, by Day, Sample Name = BRLT2



Linear Fit: Percent from Baseline = 100.3772 + 0.0981402*Day

Summary of Fit

RSquare	0.292935
RSquare Adj	0.270126
Root Mean Square Error	3.398168
Mean of Response	103.3749
Observations (or Sum Wgts)	33

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	100.3772	<.0001*	98.287696	102.46671
Day	0.0981402	0.0011*	0.0422884	0.1539919

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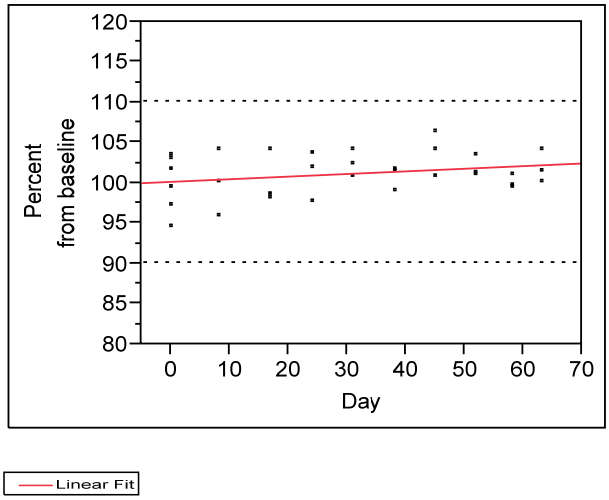
Figure A6- 3: Access 2 Calibrator Open-vial Bivariate Fit of Percent from Baseline, by Day, Sample Name = BRLT3



Linear Fit: Percent from Baseline = 100.24066 + 0.0309523*Day

Summary of Fit

RSquare	0.065643
RSquare Adj	0.035502
Root Mean Square Error	2.602621
Mean of Response	101.1861
Observations (or Sum Wgts)	33

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	100.24066	<.0001*	98.64033	101.841
Day	0.0309523	0.1501	-0.011824	0.0737286

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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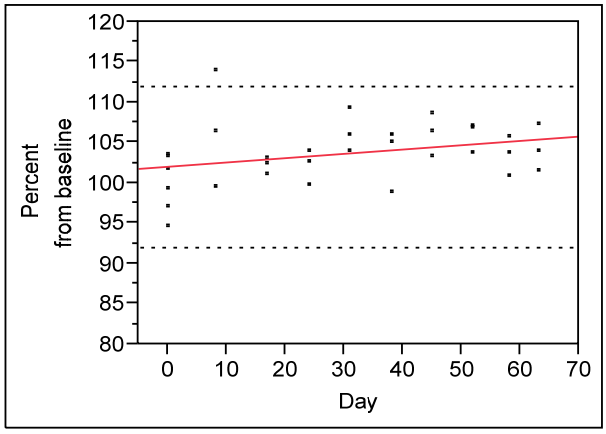
Figure A6-4: Access 2 Calibrator Open-vial Bivariate Fit of Percent from Baseline, by Day, Sample Name = MORE 3



Linear Fit

Linear Fit: Percent from Baseline = 101.99604 + 0.0554574*Day

Summary of Fit

RSquare	0.104005
RSquare Adj	0.075102
Root Mean Square Error	3.627771
Mean of Response	103.69
Observations (or Sum Wgts)	33

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	101.99604	<.0001*	99.765353	104.22673
Day	0.0554574	0.0672	-0.004168	0.1150829

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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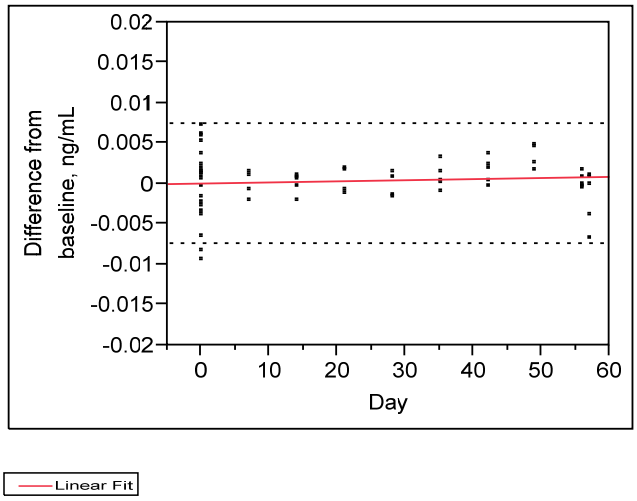
Figure A6-5: Access 2 Stored Calibration Curve Bivariate Fit of Difference from Baseline, ng/mL, by Day, Sample Name = TnI QCPT1



Linear Fit: Difference from Baseline, ng/mL = 0.0001287 + 0.0000142*Day

Summary of Fit

RSquare	0.009993
RSquare Adj	-0.00501
Root Mean Square Error	0.003069
Mean of Response	0.000451
Observations (or Sum Wgts)	68

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	0.0001287	0.8133	-0.000955	0.0012126
Day	0.0000142	0.4173	-2.053e-5	4.8929e-5

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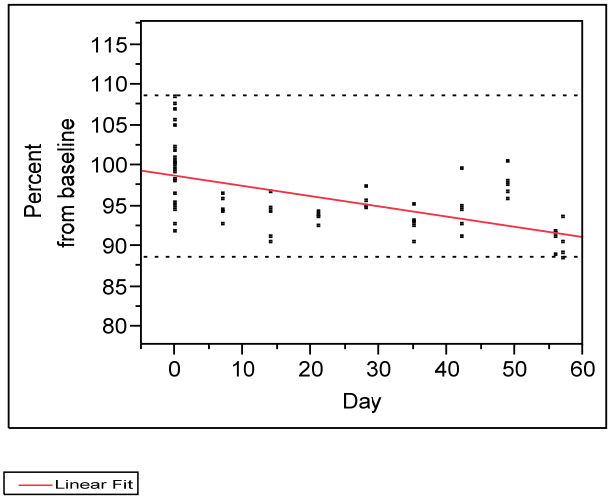
Figure A6- 6: Access 2 Stored Calibration Curve Bivariate Fit of Percent from Baseline, by Day, Sample Name = Cardiac MORE 2



Linear Fit: Percent from Baseline = 98.64526 - 0.1247772*Day

Summary of Fit

RSquare	0.337035
RSquare Adj	0.326835
Root Mean Square Error	3.79692
Mean of Response	95.76794
Observations (or Sum Wgts)	67

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	98.64526	<.0001*	97.282347	100.00817
Day	-0.124777	<.0001*	-0.168128	-0.081427

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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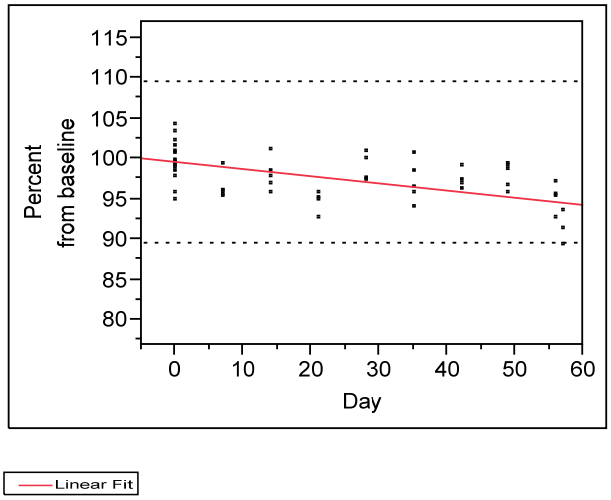
Figure A6- 7: Access 2 Stored Calibration Curve Bivariate Fit of Percent from Baseline, by Day, Sample Name = Cardiac MORE 3



Linear Fit" Percent from Baseline = 99.481836 - 0.0876444*Day

Summary of Fit

RSquare	0.353901
RSquare Adj	0.343961
Root Mean Square Error	2.569339
Mean of Response	97.46078
Observations (or Sum Wgts)	67

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.481836	<.0001*	98.559566	100.40411
Day	-0.087644	<.0001*	-0.116979	-0.05831

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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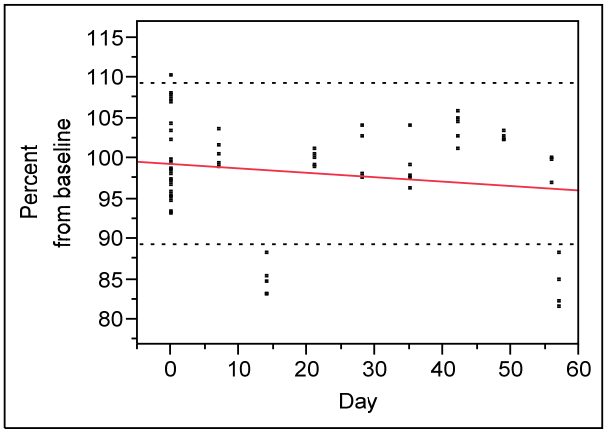
Figure A6-8: Access 2 Stored Calibration Curve Bivariate Fit of Percent from Baseline by Day, Sample Name=TnI QCPT2B



Linear Fit

Linear Fit: Percent from Baseline = 99.287315 - 0.0531017*Day

Summary of Fit

RSquare	0.029255
RSquare Adj	0.014547
Root Mean Square Error	6.642323
Mean of Response	98.08081
Observations (or Sum Wgts)	68

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.287315	<.0001*	96.941314	101.63332
Day	-0.053102	0.1631	-0.128276	0.022073

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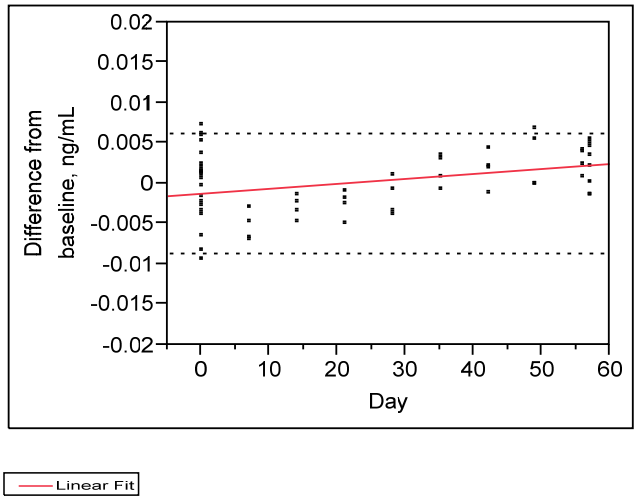
Figure A6-9: Access 2 Open Reagent Pack Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample Name=TnI QCPT1



Linear Fit: Difference from Baseline, ng/mL = -0.001328 + 0.000062*Day

Summary of Fit

RSquare	0.133632
RSquare Adj	0.119429
Root Mean Square Error	0.003613
Mean of Response	0.000112
Observations (or Sum Wgts)	63

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	-0.001328	0.0466*	-0.002636	-2.058e-5
Day	0.000062	0.0032*	2.158e-5	0.0001024

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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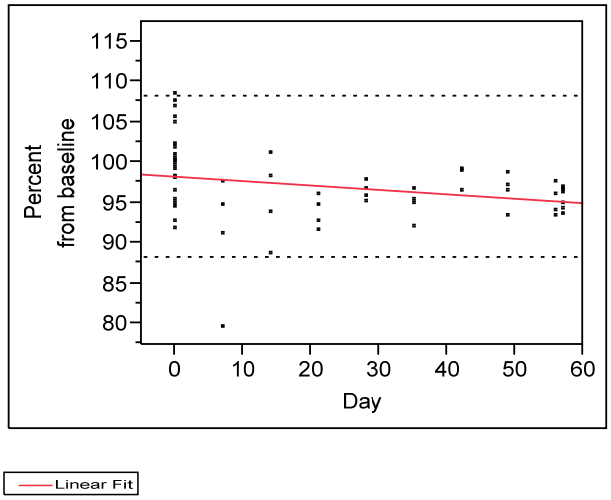
Figure A6-10: Access 2 Open Reagent Pack Bivariate Fit of Percent from Baseline by Day, Sample Name= MORE 2



Linear Fit: Percent from Baseline = 98.223772 - 0.0558867*Day

Summary of Fit

RSquare	0.076937
RSquare Adj	0.061553
Root Mean Square Error	4.428849
Mean of Response	96.90412
Observations (or Sum Wgts)	62

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	98.223772	<.0001*	96.593081	99.854462
Day	-0.055887	0.0291*	-0.105876	-0.005898

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8146

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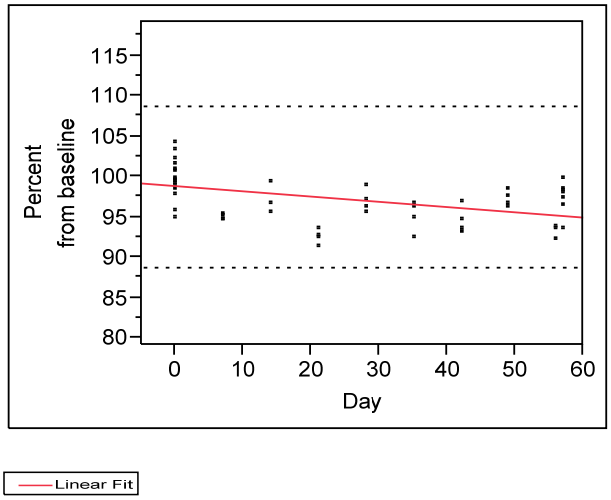
Figure A6-11: Access 2 Open Reagent Pack Bivariate Fit of Percent from Baseline by Day, Sample Name= MORE 3



Linear Fit: Percent from Baseline = 98.737942 - 0.0641329*Day

Summary of Fit

RSquare	0.231676
RSquare Adj	0.21887
Root Mean Square Error	2.672076
Mean of Response	97.22358
Observations (or Sum Wgts)	62

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	98.737942	<.0001*	97.754091	99.721793
Day	-0.064133	<.0001*	-0.094293	-0.033973

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8146

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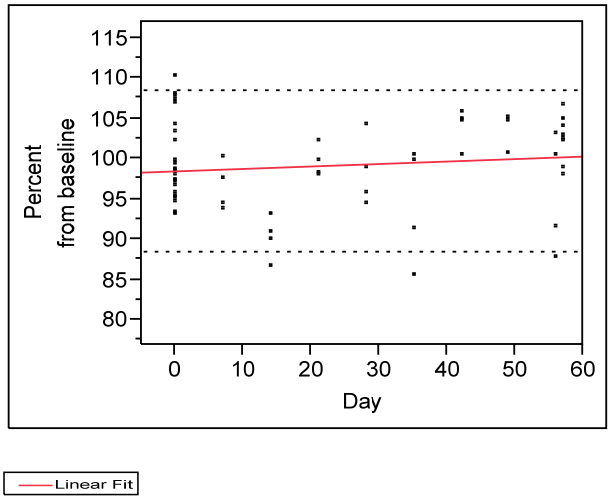
Figure A6-12: Access 2 Open Reagent Pack Bivariate Fit of Percent from Baseline by Day, Sample Name = TnI QCPT2B



Linear Fit: Percent from Baseline = 98.420776 + 0.0308885*Day

Summary of Fit

RSquare	0.016446
RSquare Adj	0.000322
Root Mean Square Error	5.467322
Mean of Response	99.13857
Observations (or Sum Wgts)	63

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	98.420776	<.0001*	96.441651	100.3999
Day	0.0308885	0.3165	-0.030269	0.0920461

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8116

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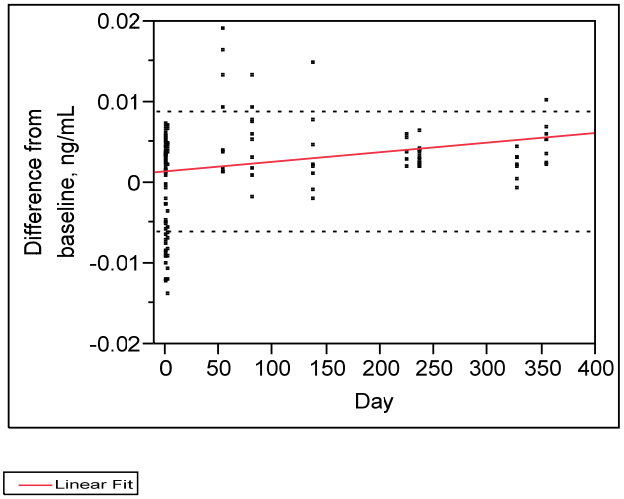
Figure A6-13: Access 2 Reagent Pack Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = MORE1, Pack lot/cal lot = 116676



Linear Fit: Difference from Baseline, ng/mL = 0.0014667 + 1.2044e-5*Day

Summary of Fit

RSquare	0.04616
RSquare Adj	0.039715
Root Mean Square Error	0.006879
Mean of Response	0.002611
Observations (or Sum Wgts)	150

Parameter Estimates

Term	Estimate	Std Error	Lower 95%	Upper 95%
Intercept	0.0014667	0.000706	7.1635e-5	0.0028618
Day	1.2044e-5	4.5e-6	3.1508e-6	2.0937e-5

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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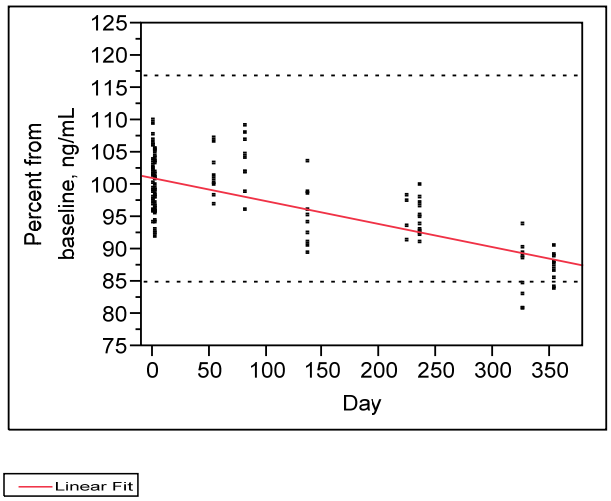
Figure A6-14: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = MORE2, Pack lot/cal lot = 116676



Linear Fit: Percent from Baseline, ng/mL = 100.945 - 0.0355395*Day

Summary of Fit

RSquare	0.505252
RSquare Adj	0.501909
Root Mean Square Error	4.418905
Mean of Response	97.56756
Observations (or Sum Wgts)	150

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	100.945	<.0001*	100.04886	101.84115
Day	-0.03554	<.0001*	-0.041252	-0.029827

Questions? Contact FDA/CDRH/OIDE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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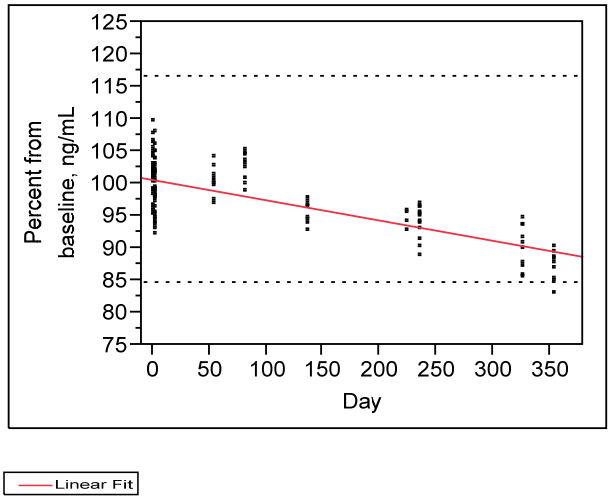
Figure A6-15: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = MORE3, Pack lot/cal lot = 116676



Linear Fit: Percent from Baseline, ng/mL = 100.62579 - 0.0317989*Day

Summary of Fit

RSquare	0.557322
RSquare Adj	0.55433
Root Mean Square Error	3.560963
Mean of Response	97.60383
Observations (or Sum Wgts)	150

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	100.62579	<.0001*	99.903629	101.34794
Day	-0.031799	<.0001*	-0.036402	-0.027195

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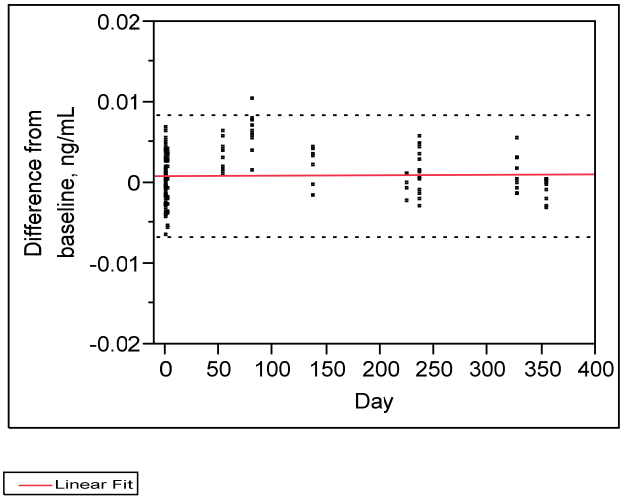
Figure A6-15: Access 2 Reagent Pack Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = BRLT1, Pack lot/cal lot = 116676



Linear Fit: Difference from Baseline, ng/mL = 0.0008663 + 6.5066e-7*Day

Summary of Fit

RSquare	0.000627
RSquare Adj	-0.00613
Root Mean Square Error	0.003265
Mean of Response	0.000928
Observations (or Sum Wgts)	150

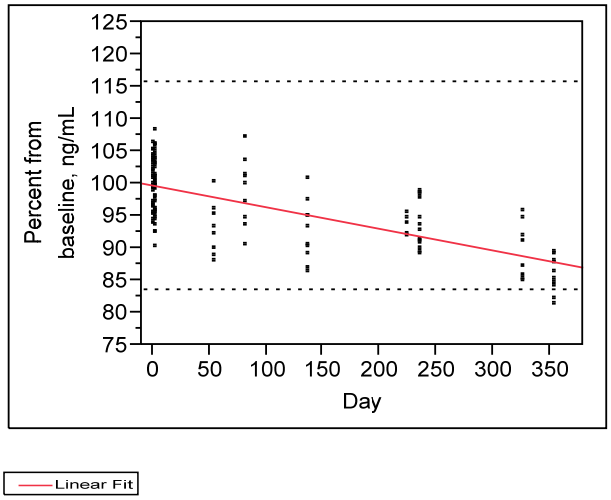
Parameter Estimates

Term	Estimate	Std Error	Lower 95%	Upper 95%
Intercept	0.0008663	0.000335	0.0002042	0.0015283
Day	6.5066e-7	2.136e-6	-3.57e-6	4.871e-6

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-16: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = BRLT2, Pack lot/cal lot = 116676



Linear Fit: Percent from Baseline, ng/mL = 99.700552 - 0.0336738*Day

Summary of Fit

RSquare	0.502412
RSquare Adj	0.49905
Root Mean Square Error	4.210769
Mean of Response	96.50042
Observations (or Sum Wgts)	150

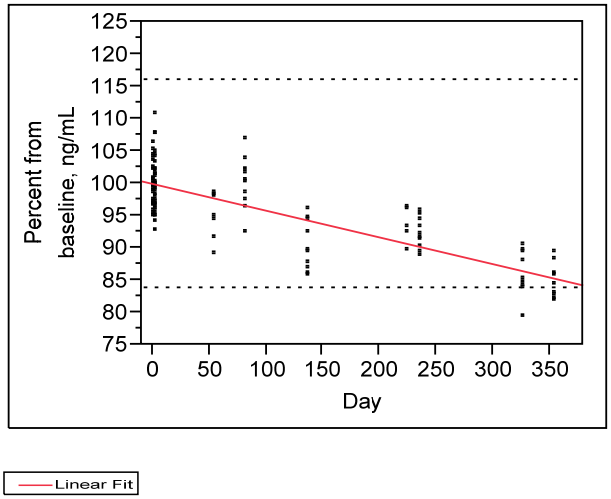
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.700552	<.0001*	98.846615	100.55449
Day	-0.033674	<.0001*	-0.039117	-0.02823

Questions? Contact FDA/CDRH/OCE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-17: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = BRLT3, Pack lot/cal lot = 116676



Linear Fit: Percent from Baseline, ng/mL = 99.952962 - 0.0412254*Day

Summary of Fit

RSquare	0.630992
RSquare Adj	0.628498
Root Mean Square Error	3.961283
Mean of Response	96.03517
Observations (or Sum Wgts)	150

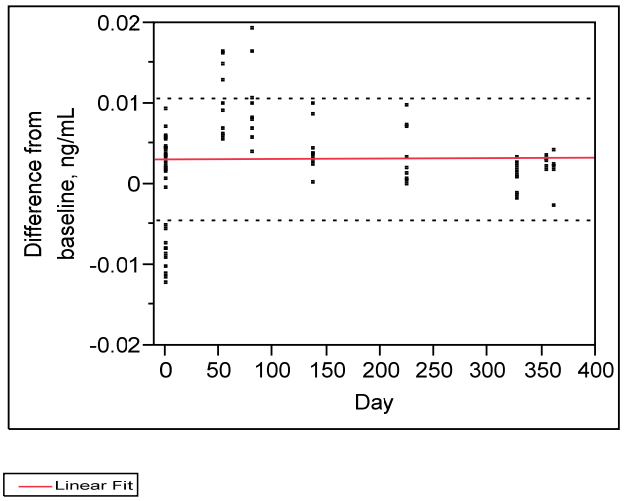
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.952962	<.0001*	99.14962	100.7563
Day	-0.041225	<.0001*	-0.046346	-0.036104

Questions? Contact FDA/CDRH/OIDE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-18: Access 2 Reagent Pack Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = MORE1, Pack lot/cal lot = 116677



Linear Fit: Difference from Baseline, ng/mL = 0.0030509 + 6.3144e-7*Day

Summary of Fit

RSquare	0.00016
RSquare Adj	-0.01004
Root Mean Square Error	0.006638
Mean of Response	0.003125
Observations (or Sum Wgts)	100

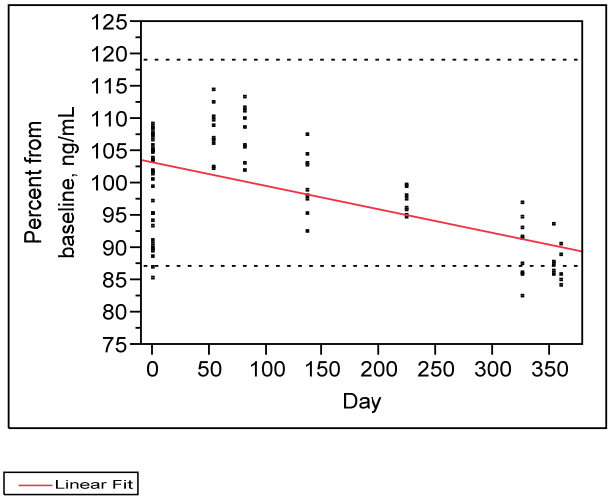
Parameter Estimates

Term	Estimate	Std Error	Lower 95%	Upper 95%
Intercept	0.0030509	0.000891	0.0012827	0.004819
Day	6.3144e-7	5.035e-6	-9.36e-6	1.0623e-5

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-19: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = MORE2, Pack lot/cal lot = 116677



Linear Fit: Percent from Baseline, ng/mL = 103.2191 - 0.0359976*Day

Summary of Fit

RSquare	0.339253
RSquare Adj	0.33251
Root Mean Square Error	6.690449
Mean of Response	98.96959
Observations (or Sum Wgts)	100

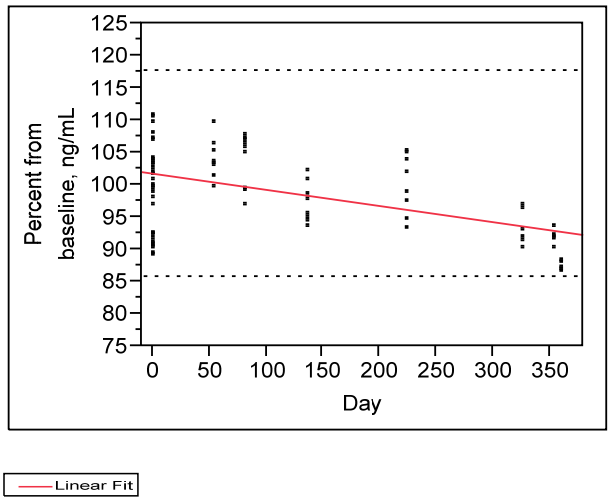
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	103.2191	<.0001*	101.43693	105.00128
Day	-0.035998	<.0001*	-0.046068	-0.025927

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-20: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = MORE3, Pack lot/cal lot = 116677



Linear Fit: Percent from Baseline, ng/mL = 101.74471 - 0.0251219*Day

Summary of Fit

RSquare	0.264743
RSquare Adj	0.25724
Root Mean Square Error	5.575524
Mean of Response	98.77908
Observations (or Sum Wgts)	100

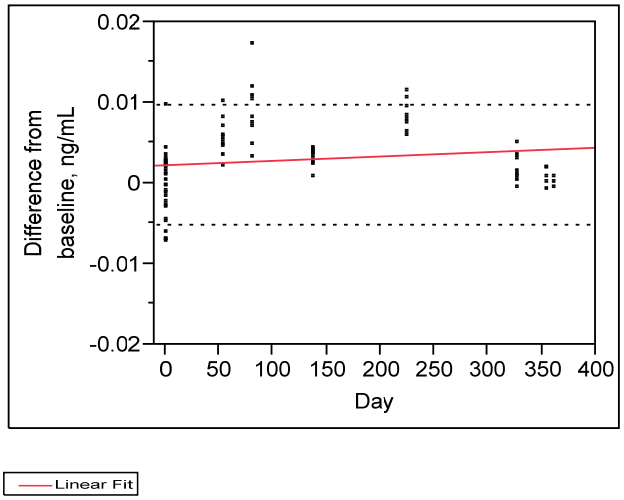
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	101.74471	<.0001*	100.25953	103.2299
Day	-0.025122	<.0001*	-0.033514	-0.016729

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8146

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-21: Access 2 Reagent Pack Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = BRLT1, Pack lot/cal lot = 116677



Linear Fit: Difference from Baseline, ng/mL = 0.0022743 + 5.5449e-6*Day

Summary of Fit

RSquare	0.027858
RSquare Adj	0.017835
Root Mean Square Error	0.004309
Mean of Response	0.002915
Observations (or Sum Wgts)	99

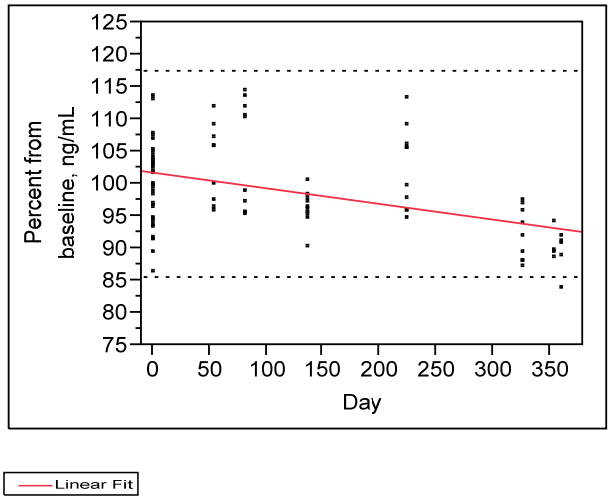
Parameter Estimates

Term	Estimate	Std Error	Lower 95%	Upper 95%
Intercept	0.0022743	0.000579	0.001125	0.0034237
Day	5.5449e-6	3.326e-6	-1.056e-6	1.2146e-5

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6- 22: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = BRLT2, Pack lot/cal lot = 116677



Linear Fit: Percent from Baseline, ng/mL = 101.62389 - 0.0242001*Day

Summary of Fit

RSquare	0.202651
RSquare Adj	0.194515
Root Mean Square Error	6.392822
Mean of Response	98.76707
Observations (or Sum Wgts)	100

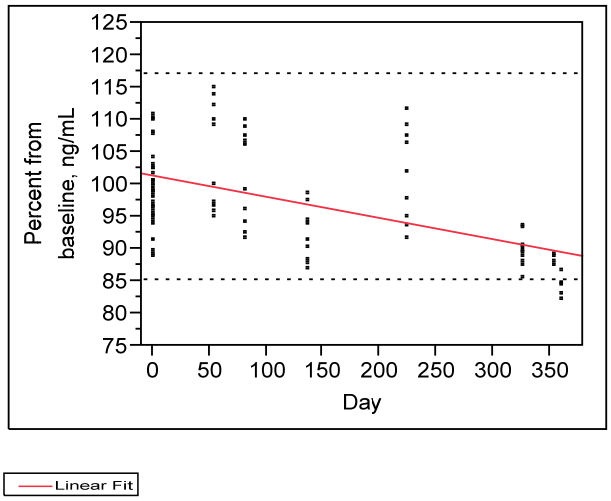
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	101.62389	<.0001*	99.921002	103.32679
Day	-0.0242	<.0001*	-0.033823	-0.014577

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-23: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = BRLT3, Pack lot/cal lot = 116677



Linear Fit: Percent from Baseline, ng/mL = 101.28338 - 0.0327695*Day

Summary of Fit

RSquare	0.258771
RSquare Adj	0.251207
Root Mean Square Error	7.386086
Mean of Response	97.41494
Observations (or Sum Wgts)	100

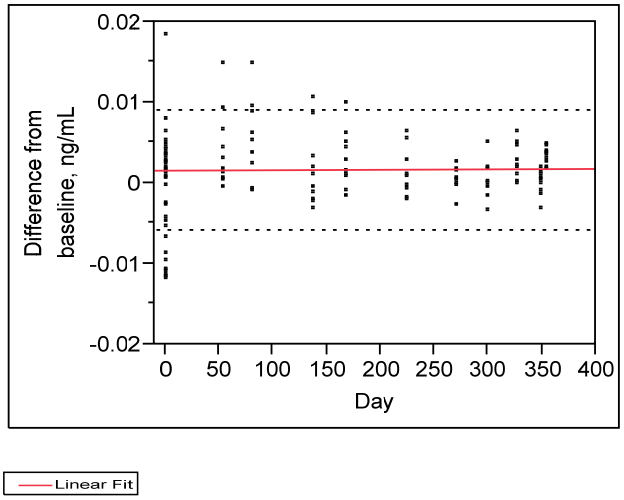
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	101.28338	<.0001*	99.315905	103.25085
Day	-0.032769	<.0001*	-0.043887	-0.021652

Questions? Contact FDA/CDRH/OIE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-24: Access 2 Reagent Pack Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = MORE1, Pack lot/cal lot = 116678



Linear Fit: Difference from Baseline, ng/mL = 0.0016697 + 5.1924e-7*Day

Summary of Fit

RSquare	0.000189
RSquare Adj	-0.00706
Root Mean Square Error	0.005153
Mean of Response	0.001754
Observations (or Sum Wgts)	140

Parameter Estimates

Term	Estimate	Std Error	Lower 95%	Upper 95%
Intercept	0.0016697	0.000678	0.0003294	0.00301
Day	5.1924e-7	3.214e-6	-5.835e-6	6.8735e-6

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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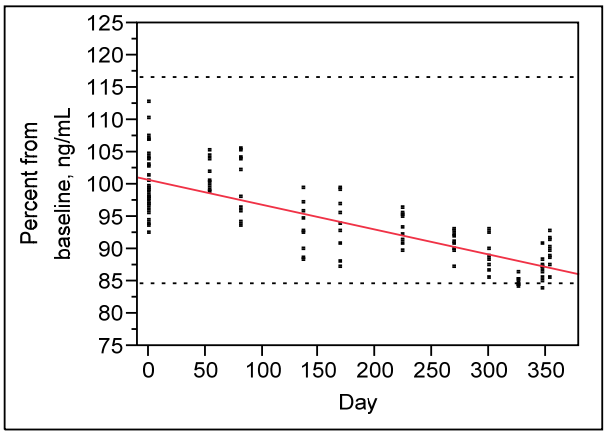
Figure A6-25: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = MORE2, Pack lot/cal lot = 116678



Linear Fit

Linear Fit: Percent from Baseline, ng/mL = 100.73334 - 0.0381641*Day

Summary of Fit

RSquare	0.659065
RSquare Adj	0.656595
Root Mean Square Error	3.746589
Mean of Response	94.56438
Observations (or Sum Wgts)	140

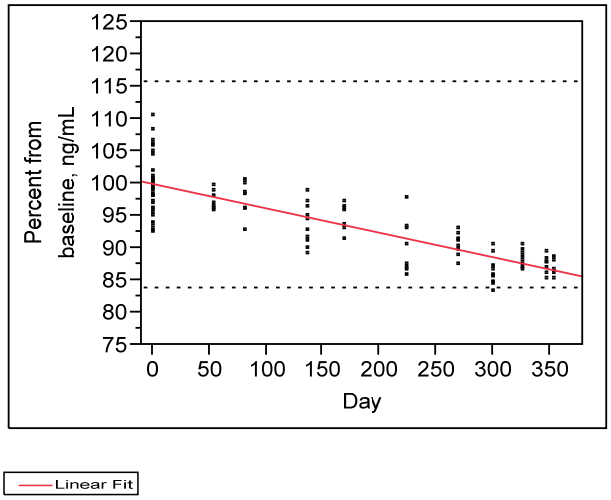
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	100.73334	<.0001*	99.758785	101.70789
Day	-0.038164	<.0001*	-0.042784	-0.033544

Questions? Contact FDA/CDRH/OIDE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-26: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = MORE3, Pack lot/cal lot = 116678



Linear Fit: Percent from Baseline, ng/mL = 99.865061 - 0.0376659*Day

Summary of Fit

RSquare	0.721698
RSquare Adj	0.719681
Root Mean Square Error	3.192554
Mean of Response	93.77663
Observations (or Sum Wgts)	140

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.865061	<.0001*	99.034625	100.6955
Day	-0.037666	<.0001*	-0.041603	-0.033729

Questions? Contact FDA/CDRH/OIE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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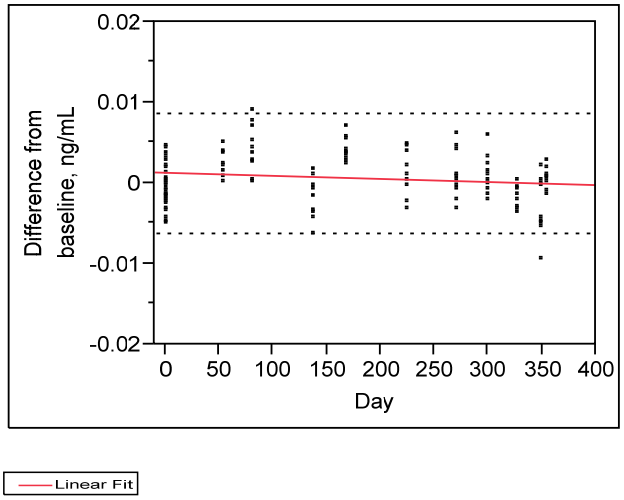
Figure A6-27: Access 2 Reagent Pack Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = BRLT1, Pack lot/cal lot = 116678



Linear Fit" Difference from Baseline, ng/mL = 0.0012302 - 3.4051e-6*Day

Summary of Fit

RSquare	0.021814
RSquare Adj	0.014726
Root Mean Square Error	0.003112
Mean of Response	0.00068
Observations (or Sum Wgts)	140

Parameter Estimates

Term	Estimate	Std Error	Lower 95%	Upper 95%
Intercept	0.0012302	0.000409	0.0004206	0.0020397
Day	-3.405e-6	1.941e-6	-7.243e-6	4.3293e-7

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8116 Page 16

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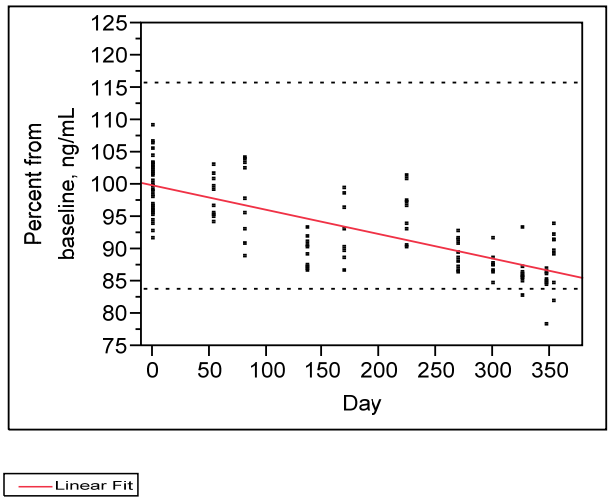
Figure A6-28: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = BRLT2, Pack lot/cal lot = 116678



Linear Fit: Percent from Baseline, ng/mL = 99.80085 - 0.037675*Day

Summary of Fit

RSquare	0.586365
RSquare Adj	0.583346
Root Mean Square Error	4.305182
Mean of Response	93.76146
Observations (or Sum Wgts)	139

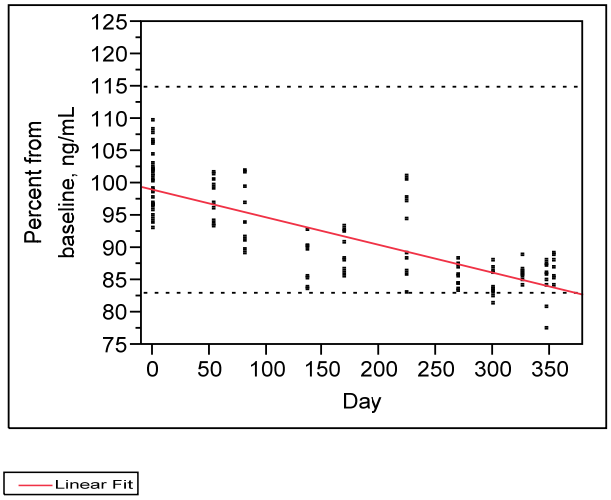
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.80085	<.0001*	98.680237	100.92146
Day	-0.037675	<.0001*	-0.043021	-0.032329

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8146

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-29: Access 2 Reagent Pack Real Time Bivariate Fit of Percent from Baseline, ng/mL by Day, Sample = BRLT3, Pack lot/cal lot = 116678



Linear Fit: Percent from Baseline, ng/mL = 99.118837 - 0.0430363*Day

Summary of Fit

RSquare	0.666417
RSquare Adj	0.664
Root Mean Square Error	4.155978
Mean of Response	92.16232
Observations (or Sum Wgts)	140

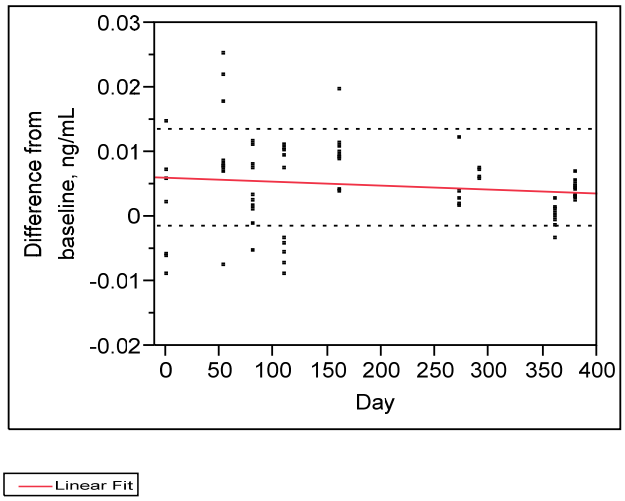
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	99.118837	<.0001*	98.037798	100.19988
Day	-0.043036	<.0001*	-0.048161	-0.037911

Questions? Contact FDA/CDRH/OIDE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-30: Access 2 Calibrator Real Time Bivariate Fit of Difference from Baseline, ng/mL by Day, Sample = MORE1, Pack lot/cal lot = 117302



Linear Fit: Difference from Baseline, ng/mL = 0.0060533 - 6.4134e-6*Day

Summary of Fit

RSquare	0.012155
RSquare Adj	-0.00051
Root Mean Square Error	0.007911
Mean of Response	0.00491
Observations (or Sum Wgts)	80

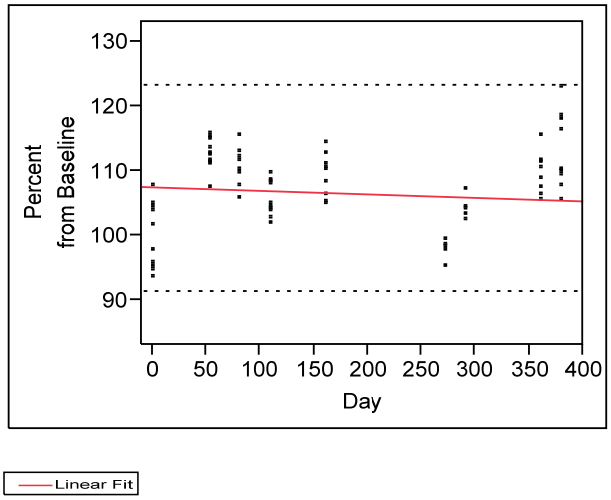
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	0.0060533	<.0001*	0.0031382	0.0089683
Day	-6.413e-6	0.3303	-1.945e-5	6.6196e-6

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8146

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-31: Access 2 Calibrator Real Time Bivariate Fit of Percent from Baseline by Day, Sample = MORE2, Pack lot/cal lot = 117302



Linear Fit: Percent from Baseline = 107.39883 - 0.0053945*Day

Summary of Fit

RSquare	0.003366
RSquare Adj	-0.00941
Root Mean Square Error	12.70134
Mean of Response	106.4373
Observations (or Sum Wgts)	80

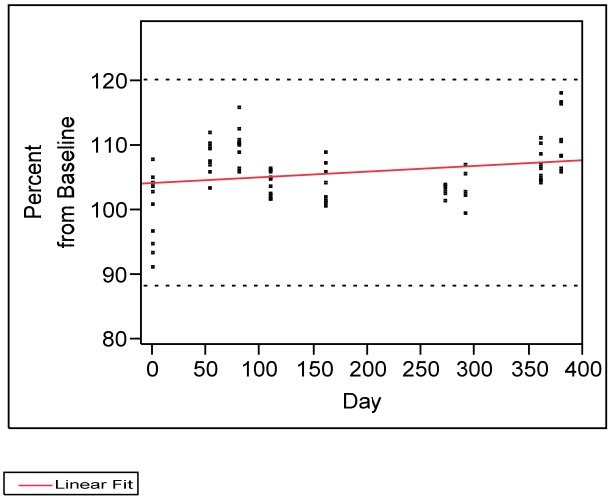
Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	107.39883	<.0001*	102.71864	112.07902
Day	-0.005394	0.6092	-0.026319	0.0155303

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Figure A6-32: Access 2 Calibrator Real Time Bivariate Fit of Percent from Baseline by Day, Sample = MORE3, Pack lot/cal lot = 117302



Linear Fit: Percent from Baseline = 104.16643 + 0.0092029*Day

Summary of Fit

RSquare	0.067403
RSquare Adj	0.055447
Root Mean Square Error	4.68393
Mean of Response	105.8068
Observations (or Sum Wgts)	80

Parameter Estimates

Term	Estimate	Prob>|t|	Lower 95%	Upper 95%
Intercept	104.16643	<.0001*	102.4405	105.89236
Day	0.0092029	0.0200*	0.0014864	0.0169194

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(1)(b) FDA: Please reanalyze all of the studies presented in page 3 table 1-1 of your response excluding samples with troponin values below your LoQ (see item 2 below) and provide an updated table 1-1 for FDA review. FDA notes that based on the current analysis, the pre-verification concordance studies seem to show a positive bias in the slope between the temperature extremes (i.e., 18 to 26°C and 22 to 26°C). Meanwhile, the repeated concordance study seems to show a negative bias in the slope between the temperature extremes. If following the requested reanalysis you observe the same trend, please explain this trend and explain why you believe it will not impact the safe use of your device on patients.

BEC Response to Question 1(b).

The original "Table 1-1" referred to in question 1(b) is provided in **Table 1-1** below:

Table 1-1: Passing-Bablok Analysis of Singlicate Results at Incremental Temperatures

Study	Low Temp	High Temp	N	Slope	Slope 95% CI	Intercept	Intercept 95% CI	R^2
Pre-verification Concordance Study	18 °C	26 °C	98	1.07	(1.04, 1.10)	0.00	(0.00, 0.00)	0.98
	18 °C	22 °C	100	1.01	(1.00, 1.03)	0.00	(0.00, 0.00)	0.99
	22 °C	26 °C	98	1.06	(1.05, 1.08)	0.00	(0.00, 0.00)	0.99
	20 °C	28 °C	100	1.00	(0.96, 1.03)	0.00	(0.00, 0.00)	0.98
	20 °C	24 °C	100	0.99	(0.97, 1.01)	0.00	(0.00, 0.00)	0.99
	24 °C	28 °C	100	1.01	(0.99, 1.04)	0.00	(0.00, 0.00)	0.99
Thermal Sensitivity – Impact on Low Dose Concordance/Agreement: Repeat Study	18 °C	26 °C	109	0.95	(0.93, 0.98)	0.00	(0.00, 0.00)	0.97
	18 °C	22 °C	108	0.99	(0.97, 1.00)	0.00	(0.00, 0.00)	0.98
	22 °C	26 °C	108	0.97	(0.95, 0.99)	0.00	(0.00, 0.00)	0.99
	20 °C	28 °C	110	0.98	(0.95, 1.00)	0.00	(0.00, 0.00)	0.99
	20 °C	24 °C	110	1.00	(0.98, 1.02)	0.00	(0.00, 0.00)	0.99
	24 °C	28 °C	110	0.97	(0.95, 1.00)	0.00	(0.00, 0.00)	0.99
Additional Concordance Studies - Overall	18 °C	28 °C	433	0.96	(0.95, 0.97)	0.00	(0.00, 0.00)	0.99
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Low Dose***	18 °C	28 °C	48	1.02	(0.98, 1.06)	0.00	(0.00, 0.00)	0.99
	18 °C	23 °C	48	0.98	(0.94, 1.01)	0.00	(0.00, 0.00)	0.99
	23 °C	28 °C	48	1.04	(1.02, 1.07)	0.00	(0.00, 0.00)	0.99
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Full Range***	18 °C	28 °C	108	0.98	(0.98, 0.99)	0.00	(0.00, 0.00)	1.00
	18 °C	23 °C	108	1.01	(1.00, 1.03)	0.00	(0.00, 0.00)	1.00
	23 °C	28 °C	108	0.97	(0.95, 0.98)	0.00	(0.00, 0.01)	0.99

All studies presented in the original table above have been reanalyzed following exclusion of samples with troponin values below the 20% CV limit of quantitation (LoQ) of 0.02 ng/mL for AccuTnI+3; the "Amended Table 1-1," following exclusion of those samples, is provided in **Table 1-2** below:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Table 1-2: Amended Table 1-1. Passing-Bablok Analysis of Singlicate Results ≥ 0.02 ng/mL at Incremental Temperatures

Study	Low Temp	High Temp	N	Slope	Slope 95% CI	Intercept	Intercept 95% CI	R^2
Pre-verification Concordance Study	18 °C	26 °C	57	1.04	(1.00, 1.08)	0.01	(0.00, 0.01)	0.97
	18 °C	22 °C	59	1.00	(0.97, 1.02)	0.00	(0.00, 0.00)	0.99
	22 °C	26 °C	57	1.05	(1.02, 1.08)	0.00	(0.00, 0.01)	0.98
	20 °C	28 °C	61	0.97	(0.92, 1.03)	0.00	(0.00, 0.01)	0.96
	20 °C	24 °C	61	0.98	(0.95, 1.01)	0.00	(0.00, 0.00)	0.99
	24 °C	28 °C	61	1.00	(0.95, 1.04)	0.00	(0.00, 0.01)	0.98
Thermal Sensitivity – Impact on Low Dose Concordance/Agreement: Repeat Study	18 °C	26 °C	76	0.93	(0.90, 0.97)	0.00	(0.00, 0.01)	0.97
	18 °C	22 °C	75	0.99	(0.97, 1.01)	0.00	(0.00, 0.00)	0.99
	22 °C	26 °C	75	0.94	(0.91, 0.97)	0.01	(0.00, 0.01)	0.99
	20 °C	28 °C	78	0.95	(0.90, 0.98)	0.01	(0.00, 0.01)	0.99
	20 °C	24 °C	78	0.99	(0.96, 1.01)	0.00	(0.00, 0.01)	0.99
	24 °C	28 °C	78	0.96	(0.93, 0.99)	0.00	(0.00, 0.00)	0.99
Additional Concordance Studies - Overall	18 °C	28 °C	379	0.94	(0.93, 0.95)	0.00	(0.00, 0.00)	0.99
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Low Dose***	18 °C	28 °C	42	1.00	(0.96, 1.05)	0.00	(0.00, 0.00)	0.99
	18 °C	23 °C	42	0.98	(0.94, 1.02)	0.00	(0.00, 0.01)	0.99
	23 °C	28 °C	42	1.03	(1.00, 1.06)	0.00	(0.00, 0.00)	0.99
Thermal Sensitivity – Impact on Cross-Temperature Method Comparison ***Full Range***	18 °C	28 °C	102	0.98	(0.97, 0.99)	0.00	(0.00, 0.00)	1.00
	18 °C	23 °C	102	1.02	(1.00, 1.03)	0.00	(-0.01, 0.00)	1.00
	23 °C	28 °C	102	0.96	(0.95, 0.98)	0.01	(0.00, 0.01)	0.99

All nineteen AccuTnI+3 comparisons presented here meet the acceptance criteria for method comparison across temperatures (slope = 1.00 ± 0.10), both before and after exclusion of samples with troponin I concentrations below the 20% CV LoQ. The slope, intercept and correlation are presented for measurements taken at different temperatures spanning the operational ambient temperature range of AccuTnI+3. Device performance is shown both at temperature extremes and at intermediate, incremental temperatures.

FDA noted a positive bias in the Pre-verification Concordance Study when comparing results at 18 °C or 22 °C to results at 26 °C, while a negative bias was observed for the same comparisons in the Repeat Concordance Study. The difference in direction of the calculated bias of these studies is maintained following exclusion of samples below the 20% CV LoQ. When data from both studies (with results < 0.02 ng/mL excluded) are combined to generate a more substantial sample number, Passing-Bablok slopes of 0.99 and 0.99 are achieved for the 18 °C vs. 26 °C and 22 °C vs. 26 °C comparisons, respectively. The distribution of all the results is presented below in **Figure 1-1** and **Figure 1-2**, indicating an overall zero bias (slope) with a standard deviation between 3% and 4%. This distribution fits easily within the 1.00 ± 0.10 acceptance criteria.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Figure 1-1: Distribution of Slopes Originally Provided in Table 1.1

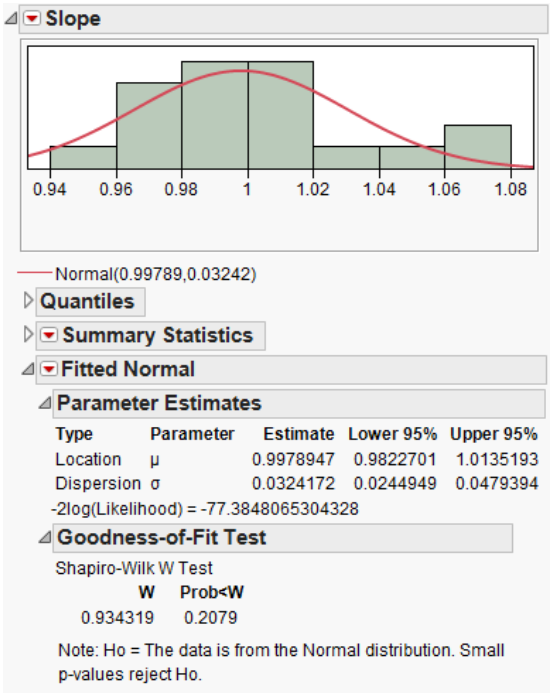
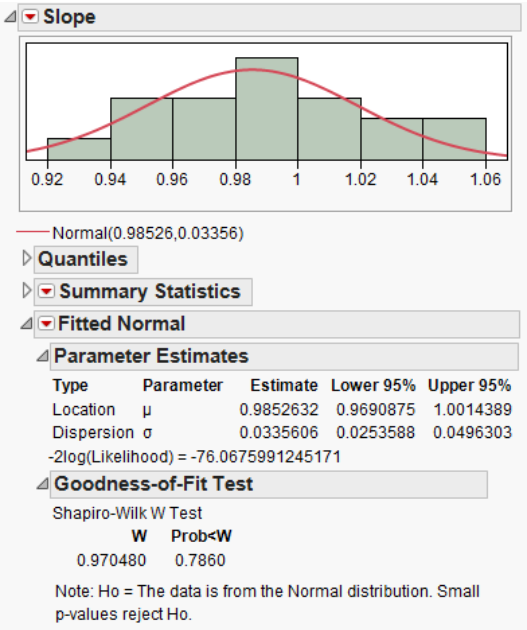


Figure 1-2: Distribution of Slopes after Excluding Samples < 0.02 ng/mL



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Conclusion: The average bias, as measured by the nineteen comparisons is zero, and the variability between comparisons is small. The individual slopes cited by the FDA in Question 1(b) are attributable to in study results, and therefore, there is no trend. The complete absence of overall bias and of bias at the individual temperature comparisons questioned by the Agency means the thermal correction algorithm has successfully eliminated detrimental thermal effects, thereby assuring the safe use of the device on patients.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 2: Limit of quantitation (LoQ)

FDA: In your new LoQ study, you measured 12 native samples and ran each sample under different conditions (3 calibration temperature, 3 ambient temperatures, 2 lots, 3 instruments and 3 days). Based on your results, you concluded that your data supports an LoQ with a precision goal of 20% CV at 0.02 ng/mL and 0.03 ng/mL with a precision goal of 10%CV. We do not concur with your conclusion. We calculated the mean, SD and %CV using all test results for each sample (that were measured around 1600 times at 3 calibration temperatures, 3 ambient temperatures, 3 instruments, 2 reagent lots, and 3 days). Here are the results of this analysis:

Sample	n	Mean ng/mL	SD	%CV
1	1617	0.011	0.004	38.8
2	1614	0.014	0.005	35.4
3	1617	0.023	0.006	26.1
4	1620	0.026	0.005	20.7
5	1617	0.037	0.003	8.7
6	1620	0.038	0.003	9.0
11	1620	0.036	0.004	10.1

This data shows that at 0.036 ng/mL your device has a 10% CV and at 0.026 ng/mL your device has a 20% CV. We obtained the same results for your low level serum samples. Please note that similar imprecision was observed in the external field effectiveness study. The %CV that we calculated for each study that used the QC sample MORE 1 (with an approximate troponin value of 0.02 ng/mL) ranged from 5.7 to 52.7% (individual %CV results: 5.7, 12.9, 14.4, 16, 20.5, 20.6, 20.8, 28, 29.1, 31.3, 32, 35, 38.5, 45 and 52.7%). Therefore, this data, in addition to our analysis of your LoQ data, do not support your current LoQ claim. Please amend your LoQ claim accordingly. Please also reevaluate your studies excluding any test result below your device's LoQ. Please provide summary data of all of your performance studies for FDA review and amend your claims if necessary.

BEC Response to Question 2.

As noted, BEC conducted a new LoQ study as requested by the Agency. This study included 11 low-concentration native lithium heparin samples and multiple variables: 3 calibration temperatures, 3 ambient run temperatures, 2 reagent lots, 3 instruments, 3 days per temperature, 2 runs per day, 10 replicates per run, resulting in a maximum of 1620 individual replicates per sample.

CLSI EP17-A2[1] allows for more than one method to statistically analyze the data used to establish the limits of detection and quantitation (LoD and LoQ). The two applicable analytical methods are the classical method and the precision profile method. For this Submission, FDA has used the classical method, and BEC has used the precision profile method. BEC strongly believes the precision profile method is more appropriate for the following reasons:

◊ BEC used the precision profile approach as described in section 6.6 of the CLSI EP17-A2 guideline. This section states that "this [approach] is particularly useful if the LoQ is determined solely on the basis of a precision requirement", and is therefore most appropriate for troponin assays[2]. Additionally, the guideline states in section 5.2 that "the precision profile approach is useful when the variability of measurement results changes significantly in the region of the assumed LoD." This is true for AccuTnI+3. See **Figure 2-1** below.

- ◊ BEC has consistently analyzed all of the LoQ studies using the precision profile method as outlined in CLSI EP17-A2. This guideline was published and approved by CLSI at the time of the original Submission. However, FDA did not recognize this released standard until January, 2013. The precision profile analysis method described in EP17-A2 was used to incorporate all experimental variables. In addition, we followed troponin NACB guidelines[3], using the recommended within-laboratory (defined as within-run and between-run) imprecision[2,4,5] calculation for all analyses submitted. Within each calibration temperature, the results of all within-laboratory imprecision estimates were combined to determine 10% CV and 20% CV LoQ.
- ◊ The analyses performed by FDA, provided in the First and Second AI Letters, have consistently used the classical LoQ analysis method described in EP17-A and EP17-A2. In the classical analysis method, the estimated LoQ is entirely dependent upon the troponin concentrations and measures of imprecision of the individual samples used in the studies. Given the rate of change of imprecision at these low levels, this method requires a significant number of samples over a limited concentration interval to obtain an accurate and reproducible estimate of the concentration at which a predefined imprecision limit occurs. Even with such a sample set, one single sample, regardless of concentration, with elevated % CV, can significantly influence and overestimate the overall LoQ estimate.
- ◊ Further, the analysis performed by FDA did not incorporate the NACB guidance to use within-laboratory imprecision estimates for troponin. The FDA analysis calculated the mean and % CV for each sample, simultaneously adding together all the variability from run, day, instrument, reagent pack, calibration, calibration temperature, and run temperature. For troponin assays, this approach to estimate imprecision is not in alignment with the recommendations or examples provided in EP17-A2 and NACB guidelines. Significantly, it does not accurately represent the performance of the device obtained in standard laboratory practice, which is more closely represented by within-laboratory imprecision.
- ◊ The robustness and reproducibility of the precision profile method of analysis is confirmed by the multiple LoQ studies conducted by BEC for AccuTnI+3:

  In the original Submission (April 20, 2012), BEC conducted 9 standardized LoQ studies, at three discrete calibration and run temperatures. BEC also conducted a multi-temperature study, incorporating multiple run temperatures. The LoQ estimates calculated by EP 17-A2, using the combined data from all run temperatures and using within-laboratory imprecision for the precision profile fit are provided in **Table 2-1**.

Table 2-1: Original Submission; Combined LoQ Results

10% CV LoQ	0.03 ng/mL
20%CV LoQ	0.01 ng/mL

In the First AI Letter, (June 20, 2012) FDA challenged our results, questioning both the test method and the use of the EP 17-A2 precision profile analysis method, which at that time was not recognized by FDA, and recommended the use of EP17-A analysis.

In the Second AI Letter (Jan 8, 2013), FDA prescribed a specific new study design and protocol for LoQ, BEC conducted a new LoB, LoD, and LoQ study, following the specified FDA protocol and submitted the results in our response to the Second AI Letter (April 23, 2013.)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

In the results of the new study included in this response to the Second AI Letter, these estimates are calculated at three calibration temperatures, across three run temperatures, and utilize within-laboratory imprecision in a precision profile analysis. These are provided in **Table 2-2**.

Table 2-2: Multi-temperature LoQ Study

Cal Temp	Run Temp	10% CV LoQ	20% CV LoQ
18ºC	18ºC, 23ºC, 28ºC	0.03	0.02
23ºC	18ºC, 23ºC, 28ºC	0.02	0.02
28ºC	18ºC, 23ºC, 28ºC	0.02	0.02

FDA agreed with the test method but did not use the EP17-A2 precision profile analysis method (which is now recognized by the Agency), and again used the classical EP17-A method for their analysis. Also, rather than using the EP17-A2 and NACB recommended within-laboratory imprecision in their calculations, FDA used an imprecision estimate that added all variabilities together.

The precision profile method of LoQ analysis provides the most representative and repeatable overall estimate of the low-end imprecision performance of the device. It provides better statistical discrimination of imprecision at specified LoQ target concentrations, and is not as sensitive to the influence of a single sample. This method aligns fully with EP17-A2 and the within-laboratory imprecision defined in the NACB guideline, which reflects routine laboratory practice: a single instrument, using a single lot of reagents, and a single stored calibration curve, to generate and report patient results. BEC firmly believes that this is the most accurate and robust representation of assay performance, and correctly reflects the low-end imprecision and LoQ for AccuTnI+3.

Conclusion: The data and discussion above supports that the AccuTnI+3 limits of quantitation are: 10% CV LoQ of 0.03 ng/mL and 20% CV LoQ of 0.02 ng/mL. However, additional analyses have been performed at the request of the Agency, which are reported in our response to Question 13. As a result of these additional analyses, BEC has revised the AccuTnI+3 limits of quantitation to: 10% CV LoQ of 0.04 ng/mL and 20% CV LoQ of 0.02 ng/mL.

We have also amended our labeling (Instructions for Use, IFU) consistent with recommendations included in CLSI EP17-A2 and the analytical measuring range (AMR) definition in the College of American Pathologists[6] (CAP) Calibrations and Standards as follows:

In Item 3 of the "Limitations of the Procedure" section in the IFU:

- The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator: 0.02 to ~100 ng/mL[µg/L].
- The analytical range of the assay is defined as the range from LoD to the S5 calibrator: 0.01 to ~100 ng/mL[µg/L].

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

- Troponin may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.

AccuTnI+3 Result (X) on Access 2	Report Result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result <0.01 ng/mL.
0.01 ng/mL (LoD) ≤ **X** < 0.02 ng/mL (20% CV LoQ)	**X** ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% CV LoQ)	**X** ng/mL.
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

In the second part of Question 2, an analysis of the field effectiveness study was performed by the FDA. This analysis assumed the MORE 1 sample was at a concentration of 0.02 ng/mL. **Table 2-3** contains the actual results from this study. Note that 12 out of the 15 results (in bold) are below 0.02. Thus, the assumption upon which the question rests is incorrect.

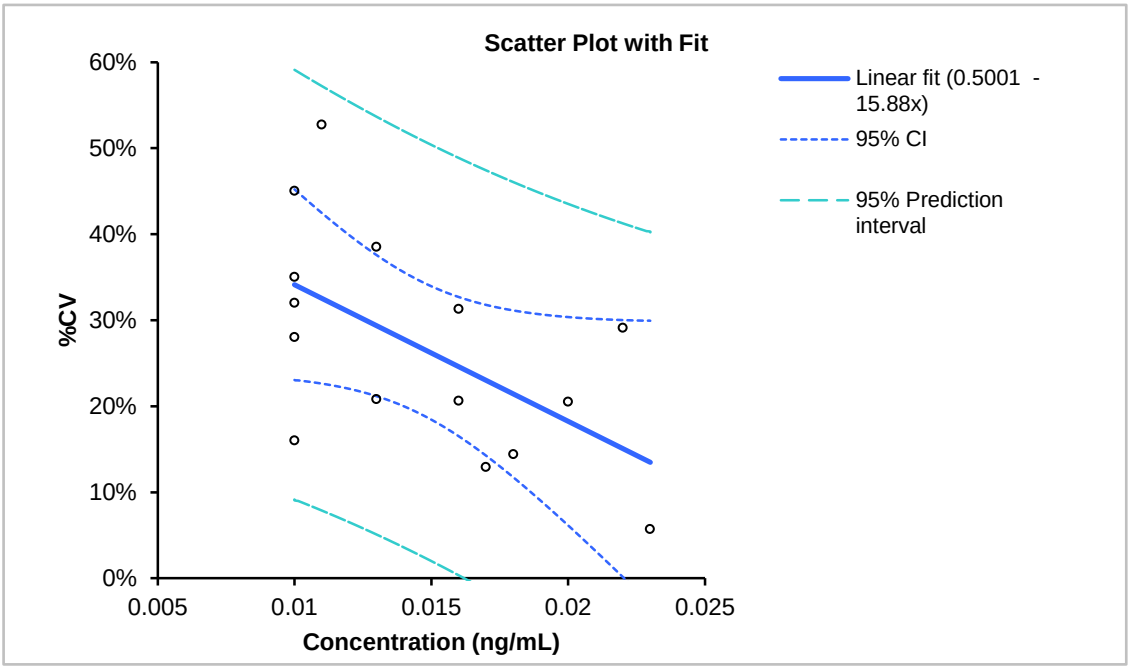
Table 2-3: More 1 Precision Results from the Field Effectiveness Study

Site	Sample	Lot	n	Concentration (ng/mL)	CV	SD
U	MORE 1	1	40	**0.016**	20.6%	0.0033
A	MORE 1	1	80	0.020	20.5%	0.0041
S	MORE 1	1	40	**0.011**	52.7%	0.0058
Q	MORE 1	1	40	0.023	5.7%	0.0013
E	MORE 1	1	36	**0.016**	31.3%	0.0050
U	MORE 1	2	40	**0.013**	20.8%	0.0027
A	MORE 1	2	62	**0.010**	28.0%	0.0028
S	MORE 1	2	40	0.022	29.1%	0.0064
Q	MORE 1	2	40	**0.018**	14.4%	0.0026
E	MORE 1	2	36	**0.013**	38.5%	0.0050
U	MORE 1	3	40	**0.010**	16.0%	0.0016
A	MORE 1	3	62	**0.010**	32.0%	0.0032
S	MORE 1	3	40	**0.010**	45.0%	0.0045
Q	MORE 1	3	40	**0.017**	12.9%	0.0022
E	MORE 1	3	36	**0.010**	35.0%	0.0035

Incorporating these results from the field effectiveness study for performing precision analyses based on CV, the plot in **Figure 2-1** below shows that %CV is negatively correlated with concentration (p=0.025).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Figure 2-1: Precision Profile



Using this precision profile, the calculated imprecision at 0.02 ng/mL is 18.3%. This supports the 20% LoQ of 0.02 ng/mL. The combined standard deviation (SD) is 0.0039. This supports the LoD of 0.01 ng/mL. This combined SD was obtained by taking the square root of the average variance as recommended in EP17-A and EP17-A2.

Conclusion: The FDA analysis from the second part of Question 2 makes an incorrect assumption on sample concentration. When the actual data is used, the results support Beckman's proposed LoD and 20% CV LoQ concentrations of 0.01ng/mL and 0.02 ng/mL, respectively.

Finally, the requested results and summary data for the nineteen reanalyzed AccuTnI+3 comparisons across temperatures, *excluding results below the 20% CV LoQ*, are presented above in our response to Question 1(b).

The requested results and summary data for the matrix comparison studies performed at 3 different ambient temperatures, *and excluding test results below the 20% CV (LoQ)*, are presented below in our response to Question 4.

For other performance studies, either there were no samples below the 20% CV LoQ (e.g., precision, cross reactivity) or the analysis of results after excluding samples below the 20% CV LoQ is not feasible because it would compromise the intent of the analysis (e.g., LoB, LoD, linearity).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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References:

[1] Pierson-Perry, JF, et. al., EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition, CLSI, Wayne, PA (2012).

[2] Ibid EP17-A2, page 29: "within laboratory precision – no associated bias goal – for cardiac troponin"

[3] Apple, FS, et. al., National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biochemical Markers of Acute Coronary Syndromes, Clinical Chemistry 53:4, 547-551 (2007).

[4] Ibid EP17-A2, page 29: "Precision estimates for LoQ application should reflect both repeatability and day-to-day variability."

[5] Krouwer, JS, et. al., EP5-A2: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline – Second Edition, CLSI, Wayne, PA (2004).

[6] College of American Pathologists, Calibration and Standards, Chemistry and Toxicology Checklist item CHM.12950, 01.04.2012

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 3: Interference

FDA: Please address the following:

(3)(a) FDA: At 0.05 ng/mL troponin, dopamine at 65 mg/dL resulted in 13.8% bias. Therefore, we recommend that you amend your dopamine interference claim (from 45 mg/dL—which was not tested at 0.05 ng/mL troponin) to 30 mg/dL.

BEC Response to Question 3(a).

The labeling has been updated to reference 30 mg/dL for dopamine interference, per FDA's request. A copy of the revised Instructions for Use (IFU) is attached in Appendix 8.

(3)(b) FDA: For Low MW Heparin, your package insert states that no in[ter]ference was observed up to 71 µg/mL. However, you tested up to 28.8 U/mL. Please clarify if these concentrations are equivalent. If not, please resolve this discrepancy.

BEC Response to Question 3(b).

Low MW heparin was tested at 28.8 U/mL. The "71 µg/mL" concentration listed in the IFU was a transcription error. BEC has removed sodium heparin from the interferences labeling, as recommended by FDA, and has corrected the labeling to reflect the actual concentration of Low MW heparin tested (28.8 U/mL).

(3)(c) FDA: Your labeling indicates that there is no interference observed up to 6 µg/dL of Nifedipine. This concentration is much lower than what you tested which was 60 µg/dL. Please clarify this discrepancy.

BEC Response to Question 3(c).

Nifedipine was tested at 60 µg/mL (6 mg/dL). The labeling (IFU) incorrectly stated that interference testing was performed at 6 µg/dL nifedipine. The IFU has been revised to reflect the actual concentration tested (60 µg/mL).

While researching the discrepancy in the Nifedipine results, we determined that the primary concentration of Simvastatin tested was 20 ug/mL, not 200 ug/mL, as stated in the IFU and reported in the Submission. The IFU has been updated to reflect the actual concentration tested in the study (20 ug/mL).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 4: Matrix comparison

FDA: Please provide regression analyses of the matrix comparison studies that you performed at 3 different ambient temperatures using singlicate test results (in accordance with the intended use of your device). Currently you provided regression analyses using duplicate results. Please also make sure to exclude any test results below your LoQ.

BEC Response to Question 4

Regression analyses of the matrix comparison studies performed at 3 different ambient temperatures using singlicate test results and excluding test results below the 20% CV limit of quantitation (LoQ) are provided below in **Table 4-1**, as requested:

Table 4-1: Lithium Heparin Plasma vs. Serum Matrix Comparison

Temperature	Data	N	Slope	95% CI Slope	Intercept	95% CI Intercept	R
18 °C	All Samples	103	1.03	(1.01, 1.06)	0.00	(-0.01, 0.00)	0.99
	Samples ≥ 0.02 ng/mL	97	1.04	(1.02, 1.07)	-0.01	(-0.01, 0.00)	0.99
23 °C	All Samples	103	1.03	(1.00, 1.05)	0.00	(-0.01, 0.00)	0.99
	Samples ≥ 0.02 ng/mL	97	1.03	(1.00, 1.05)	0.00	(-0.01, 0.00)	0.99
	*Low-range samples 0.02 - 0.50 ng/mL	43	0.98	(0.93, 1.02)	0.00	(-0.00, 0.00)	0.99
28 °C	All Samples	103	1.04	(1.02, 1.05)	0.00	(-0.01, 0.00)	0.99
	Samples ≥ 0.02 ng/mL	97	1.04	(1.02, 1.05)	0.00	(-0.01, 0.00)	0.99

Conclusion: Passing-Bablok regression analysis of singlicate results from matched lithium heparin plasma and serum samples meet the acceptance criteria for matrix comparison (slope = 1.00 +/- 0.10) at all ambient temperatures both before and after exclusion of results below the 20% CV LoQ. These data further confirm the equivalent performance of lithium heparin plasma and serum sample types on AccuTnI+3.

*The "low-range samples" data are shown here for 23 °C because this information is included in the IFU.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 5: Acceptance criteria

FDA: You have tightened your acceptance criteria for TnI concentrations ≤ 0.075 ng/mL to SD ≤ 0.006. Please provide a summary of all acceptance criteria used for the different studies for FDA review. Please make sure that your labeling is also updated with the correct acceptance criteria.

BEC Response to Question 5.

During the course of the 510(k) review process for AccuTnI+3, and as requested by the Agency, numerous analytical studies have been repeated and/or reanalyzed, and acceptance criteria have been added or tightened. BEC has prepared a summary table listing the original and revised acceptance criteria used for different studies conducted both as part of the original Submission and in response to requests from FDA for additional information. Please see the acceptance criteria table attached in Appendix 1.

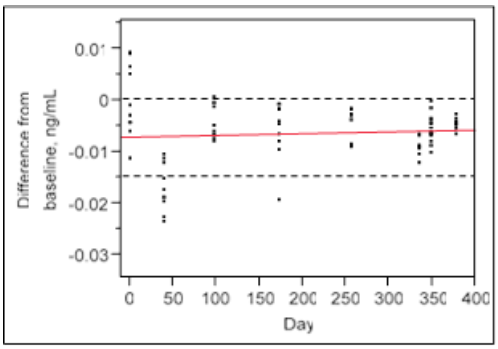
Where appropriate, we have updated our device labeling to reflect the tightened acceptance criteria.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 6: Stability

FDA: It seems that you plan to monitor acceptable stability of your calibrators based on regression analysis using samples over multiple timepoints. However, based on the graph you provided from one of your stability studies (see Figure A6-42 below) it seems that at the timepoint around 50 days, the replicates deviated significantly from the regression line. Please explain why this performance was not considered to indicate instability. We are very concerned that during the routine monitoring of the stability of your calibrators you may not identify instability until several timepoints have failed. We are concerned that this could impact patient safety. Please address this concern with your stability approach. We recommend that you develop bias and precision limits (using your new tightened acceptance criteria) for each timepoint.

Figure A6-42 from your response:



BEC Response to Question 6.

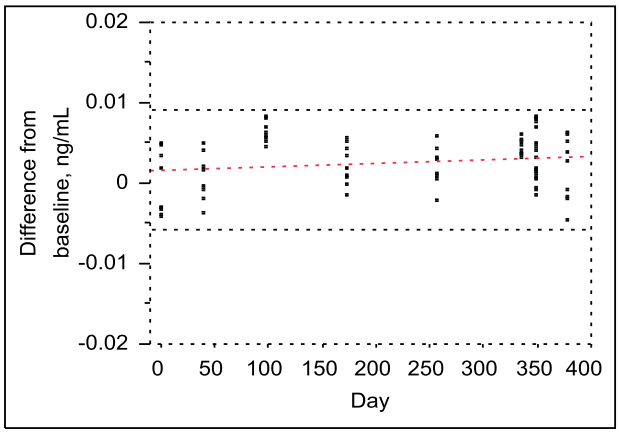
Calibrator stability studies are conducted to determine if any changes to calibrators over time lead to a change in the output (dose response) of samples and controls. The real-time stability studies presented to FDA in BEC's response to k121214-S001 were conducted over approximately 13 months, with assessments at pre-planned intervals, to support 12-month expiration dating; they were studies designed to establish the initial shelf life of the calibrators. In the example shown above, a time point at around 50 days (39 days) for one commercial control showed a difference from the baseline value. This control met the pre-established acceptance criteria at the time of the study.

An unstable calibrator or calibrator set would be expected to cause shifts in multiple samples or controls, which did not occur here. In addition, an unstable calibrator or calibrator set would not return to "normal" at subsequent time points. The calibrator cited in the question did return to normal.

For example, **Figure 6-1** below shows a different commercial control sample that was tested in the same stability study (calibrator lot 119776) as the sample shown in Figure A6-42, above and was also in the same low-dose range of the assay (≤ 0.075 ng/mL). This sample does not exhibit a similar shift at 39 days or at any other time point. The other reactive samples tested in the same run also met all acceptance criteria. Three normal samples (≤ 0.02 ng/mL) were also evaluated at each time point and met all acceptance criteria. Taken as a whole, the data set at day 39 did not indicate a stability failure for calibrator lot 119776.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Figure 6-1: The figure below is *Figure A6-45* from the Second AI Letter



For stability-monitoring studies for commercial calibrators, Beckman follows its standard process for evaluating the calibrators at each time point. Since a deviation from the expected value of a patient control sample or a commercial control at one time point could indicate an issue related to the instrument, reagent, operator, control or calibrator, the deviation is not automatically considered a calibrator stability failure. However, the deviation would trigger a failure investigation immediately, and the testing would be repeated; additional time points may be scheduled as part of the investigation. Consistent with the recommendations in CLSI EP25-A, two consecutive time point failures would be considered a stability failure and appropriate actions would be taken.

Beckman has bias criteria for samples used in a stability-monitoring study for each time point. At each time point, the samples are evaluated against pre-defined ranges, and must be within approximately 1SD (1Z) of this target. If bias criteria are not met, or if unexpected imprecision is observed among the results of a sample at a given time point, then steps are taken to address the finding, including scheduling an additional testing time point within one month and initiating a failure investigation, if appropriate.

Conclusion: BEC's stability-establishment and stability-monitoring studies use multiple patient control samples and commercial controls, and the determination of calibrator stability is based on an evaluation of the entire data set. Test conditions are set up so that a single test condition failure would not compromise the integrity of the study. Because the shift was isolated to a single sample (MORE1 control) at a single time point, there was no trend indicating that the shift at 39 days had been caused by instability of the calibrators. BEC's stability approach is adequate to ensure Access AccuTnI+3 calibrators are safe and effective for their intended use.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 7: Labeling

FDA: Please amend your labeling with the items above and also please address the following:

(7)(a) Your assay name is AccuTnI+3 but your test name is TnIA2. We are concerned that this may be confusing to the intended user and recommend that you address this apparent discrepancy in your nomenclature.

BEC Response to Question 7(a).

Our customers understand that the assay's *test name* is often different from the product's *commercial name*, and BEC does not believe there will be confusion between the commercial name, "Access AccuTnI+3 on the Access 2 Immunoassay Systems," and the test name, "TnIA2," which is selected from the menu of available assays when tests are requested.

(7)(b) You state "If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder." Please provide data for FDA review that substantiates your claim that your device will generate accurate troponin results using samples that have been frozen at -20°C or colder.

BEC Response to Question 7(b).

During the original development of AccuTnI (k010429), a sample stability study demonstrated that troponin I analyte is stable when stored at -20 °C. In 2009, that study was repeated. Data for the 2001 and 2009 studies are attached in Appendix 2 and Appendix 3, respectively.

The two antibodies in AccuTnI+3 are the same two antibodies, with the same epitope recognition, as those in the original 510(k) study and in the 2009 study. Instability of the troponin I molecule would be recognized equally by the identical antibody pair; therefore, the complete sample stability study was not repeated for AccuTnI+3.

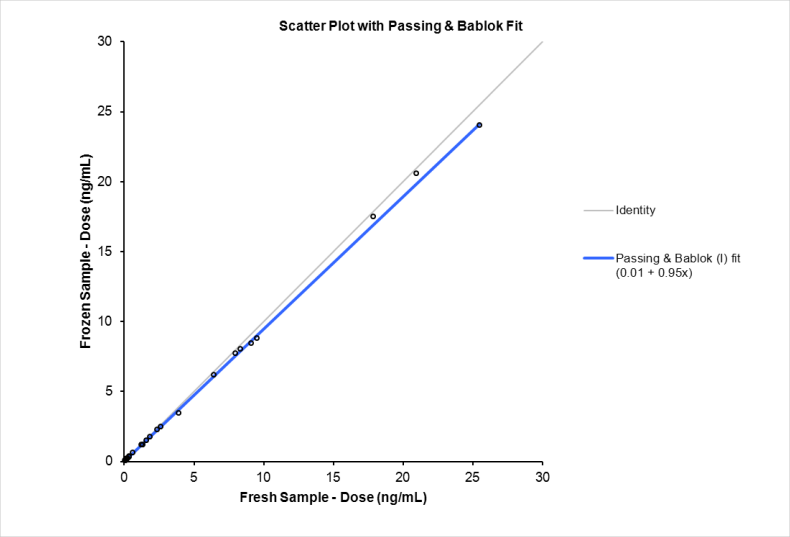
However, we have tested a small set of samples to confirm the equivalence of fresh and frozen samples once again with verification of the AccuTnI+3 assay. Freshly drawn patient samples obtained in a clinical laboratory were tested on the AccuTnI+3 assay and were subsequently retested following storage at -20 °C or colder. The Passing-Bablok results comparing fresh and frozen samples are provided below in **Table 7-1** and **Figure 7-1**.

Acceptance criteria: Passing-Bablok slope = 1.00 ±0.10.

Table 7-1: Comparison of Fresh and Frozen Troponin I Samples

N	P-B Slope	Slope 95% CI	Intercept	Intercept 95% CI	R^2
32	0.95	(0.94, 0.96)	0.01	(0.00, 0.01)	1.00

Figure 7-1: Passing-Bablok Regression of Fresh and Frozen Troponin I Samples



Conclusion: The studies described above show that the acceptance criteria have been met and demonstrate the equivalence of troponin I results, regardless of whether the samples were fresh or stored frozen. Thus, AccuTnI+3 generates accurate troponin results using samples that have been frozen at -20 °C or colder.

(7)(c) We do not agree that samples can be accurately measured within the analytical range of the assay. Please amend your labeling to indicate that samples can be accurately measured within the reportable range of the assay (which should be defined as your LoQ to 100 ng/mL).

BEC Response to Question 7(c).

We have adjusted the analytical measuring range of the assay to be from the 20% CV LoQ to ~100 ng/mL (the S5 calibrator), as you requested. The device labeling has been updated to reflect this adjustment.

(7)(d) Under expected values you state "Each laboratory should establish its own reference range to assure proper representation of specific populations and sample types and to reflect current practice at their institutions." Please remove this statement. This is not appropriate because laboratories will not know the clinical performance of the device at different cut-offs or with different sample types.

BEC Response to Question 7(d).

We have removed the statement, "Each laboratory should establish its own reference ranges to assure proper representation of specific populations and sample types, and to reflect current practice at their institutions."

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

(7)(e) Please remove the statement "each facility should evaluate the prevalence at their institution and adjust PPV and NPV accordingly" since the NPV and PPV are provided in the labeling to describe the performance of your device in your study.

BEC Response to Question 7(e).

We have removed the statement, "Each facility should evaluate prevalence at their institution and adjust PPV and NPV accordingly."

(7)(f) For your precision studies, please provide the number of days over which these studies were performed.

BEC Response to Question 7(f).

Testing for the first precision study described in the IFU was conducted over a 13-day period of time. Testing for the second study spanned 14 days. This information has been added to the IFU as requested.

(7)(g) For your instrument, please clarify if it is the Access 2 System or the Access 2 Immunoassay System. Please make sure that the name that you use is consistent in the Intended Use Form, the 510(k) Summary and in the labeling.

BEC Response to Question 7(g).

We have updated the Intended Use Form and the 510(k) Summary to be consistent with the device labeling, referring to the instrument as the "Access 2 Immunoassay System." The Intended Use Form and the 510(k) Summary are attached in Appendix 4 and Appendix 5, respectively.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 8: Clinical performance at 0.03 and 0.04 ng/mL:

FDA: It seems that the sensitivity is identical for these 2 cutoffs at the 6-9 hour timepoint. Is this correct? If not, can you please provide the correct sensitivity estimate to FDA and amend your labeling if necessary.

BEC Response to Question 8.

Yes, the data we submitted are correct.

Question 9: Standards

FDA: Please provide a list of any standards or guidance documents that you reference as part of your submission. If you used any FDA recognized documents for your studies, you will need to submit FDA form 3654 for each referenced document with your response.

BEC Response to Question 9.

The standards and guidance documents referenced as part of the Submission are shown in **Table 9-1** below. An FDA form 3654 is included with this Response in Appendix 6 for each FDA-recognized standard or guidance document upon which our study designs were based.*

Table 9-1: Referenced Standards and Guidance Documents

Document No.	Document Name	Usage
EP5-A2*	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition	Basis for precision study designs
EP6-A*	Clinical Evaluation of Immunoassays; Approved Guideline - Second Edition	Basis for linearity study designs
EP7-A2*	Interference in Clinical Chemistry; Approved Guideline - Second Edition	Basis for interference and analytical specificity study designs
EP9-A2	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition	Reference only
EP17-A2*	Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline - Second Edition	Basis for limits of detection study designs
EP24-A2	Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves.	Reference only
EP25-A*	Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.	Basis for stability study designs
C28-A3c*	Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition	Basis for reference interval trial design
I/LA21-A2	Clinical Evaluation of Immunoassays; Approved Guideline - Second Edition	Reference only

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Question 10: 510(k) Summary

FDA: Please update your 510(k) Summary with the items listed above. Please make sure to include the product codes associated with your device (i.e., MMI for troponin, JIT for your calibrator, and JJE for your instrument). In your comparison to the predicate device table, please make sure that the information included for the predicate devices is the cleared performance for each device and agrees with FDA's Decision Summary for each device.

BEC Response to Question 10.

An updated 510(k) Summary, including the product codes, is included with this Response in Appendix 5.

Question 11: Change in Correspondent

FDA: If your official correspondent has changed, please make sure to submit a letter updating the correct correspondent for this file.

BEC Response to Question 11.

BEC's letter identifying the new correspondent for this file has been attached to this Response in Appendix 7.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Question 12: (e-mailed question – 5/23/13)

FDA: Can you clarify for me how the instruments were incorporated into this design?

BEC Response to Question 12.

The three instruments were incorporated into the study design as follows: On each of the three instruments, 3 days of testing were completed with 2 runs per day and 10 replicates per run. This was repeated for each sample at each of the three temperatures. Each of these datasets was then analyzed using a calibration curve generated at each of the 3 ambient temperature set points. This analysis yielded a total of approximately 60 replicates for each sample at each calibration temperature / measurement temperature / instrument combination. As recommended by the Agency, two reagent pack lots were used for the testing with one reagent lot used on two instruments and the other reagent lot used on the third instrument. Please see **Table 12-1** below:

Table 12-1: Instruments incorporated in LoQ Design

Temperature	18 °C			23 °C			28 °C		
Instrument Number	1	2	3	1	2	3	1	2	3
Reagent Lot	1	2	1	1	2	1	1	2	1
Number of Days	3	3	3	3	3	3	3	3	3
Runs per Day	2	2	2	2	2	2	2	2	2
Reps per Run	10	10	10	10	10	10	10	10	10
Total Reps per Sample	60	60	60	60	60	60	60	60	60

Question 13: (e-mailed question – 5/24/13)

FDA: Please address the following:

(13)(a) Please provide your LoQ data (from the 11 low level patient samples calibrated at 18, 23 and 28 degrees Celsius and run at 18, 23 and 28 degrees Celsius) analyzed following the recommendations described in Appendix D "Limit of Quantitation as Functional Sensitivity" of EP17-A2. Please provide summary data for your 11 LoQ samples (Mean, SD, %CV) by reagent lot (i.e., lot 1 and lot 2), by run temperature (i.e., 18, 23 and 28 degrees—you may stratify these results by lot and present each lot separately) and by instrument (i.e., instrument 1, 2 and 3—again, you may choose to stratify by lot and present the results for each lot separately) using the exact format in Table D1 of Appendix D (i.e., the mean, SD, and %CV for each of your 11 samples). Please also plot these data exactly as shown in figure D1 of Appendix D, using the same scale for all plots. Please provide the different tables (by reagent lot, by run temperature and by instrument) and the different plots for FDA review). You should use the power function model fit line to determine the LoQ at your pre-specified precision goal. We recommend that you review these results and determine your LoQ based on these analyses.

BEC Response to Question 13(a).

Additional analyses were performed on the lithium heparin plasma Limit of Quantitation (LoQ) data as requested by the Agency. Data were analyzed following the recommendations described in Appendix D "Limit of Quantitation as Functional Sensitivity" of EP17-A2. For each sample, the within-laboratory standard deviation and %CV (within-run + between-run) were calculated and the data are presented as displayed in Table D1 of Appendix D of EP17-A2. LoQ estimates were calculated for the pre-specified precision goals of 10% CV and 20% CV.

For each sample, the mean concentration and %CV data were plotted and fit with a power function model as in Figure D1 of Appendix D of EP17-A2. The guideline states that the data be "fit by a suitable regression model or graphical interpolation," and that goodness of fit may be assessed by visual or quantitative examination. The example dataset in Appendix D uses a log-log linear power function. For AccuTnI+3, a log-log quadratic power function provides an improved fit compared to a log-log linear function, as demonstrated by the improved adjusted R-squared. For all analyses, the 10% CV and 20% CV LoQ calculated from both the linear and quadratic power function model are provided and the goodness of each fit is represented by the calculated adjusted R-squared for each.

Plasma LoQ Estimate Analyses:

The above method of analysis was completed for the LoQ data following stratification by the variables of reagent lot, run temperature, and instrument. Summary data by reagent lot is provided in **Table 13-1** and **Figure 13-1** and **Figure 13-2**. Summary data by run temperature is provided in **Table 13-2** and **Figure 13-3**, **Figure 13-4**, and **Figure 13-5**. Summary data by instrument is provided in **Table 13-3** and **Figure 13-6**, **Figure 13-7**, and **Figure 13-8**. Finally, a summary of all calculated 10% CV and 20% CV LoQ results are provided in **Table 13-4**.

Table 13-1: Plasma LoQ Summary by Reagent Lot

	Reagent Lot 225961			Reagent Lot 225962		
Sample Pool Identification	Mean (ng/mL)	SD_{WL} (ng/mL)	CV (%)	Mean (ng/mL)	SD_{WL} (ng/mL)	CV (%)
Sample 001	0.012	0.003	25.0%	0.011	0.003	27.8%
Sample 002	0.015	0.004	28.9%	0.014	0.003	24.5%
Sample 003	0.023	0.005	22.9%	0.023	0.006	25.7%
Sample 004	0.026	0.004	16.3%	0.025	0.007	26.4%
Sample 011	0.035	0.003	7.4%	0.037	0.003	6.9%
Sample 005	0.036	0.002	5.8%	0.038	0.003	6.6%
Sample 006	0.037	0.002	6.1%	0.039	0.003	6.9%
Sample 007	0.053	0.003	4.9%	0.053	0.002	4.7%
Sample 008	0.063	0.004	5.7%	0.064	0.004	6.3%
Sample 009	0.136	0.006	4.2%	0.142	0.007	5.2%
Sample 010	0.248	0.007	3.0%	0.264	0.012	4.4%

Figure 13-1: Power Function Model Fits for Reagent Lot 225961

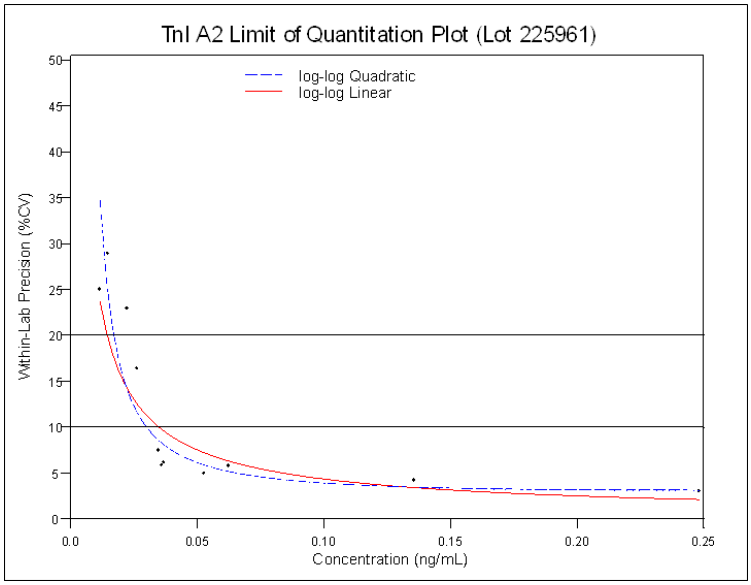


Figure 13-2: Power Function Model Fits for Reagent Lot 225962

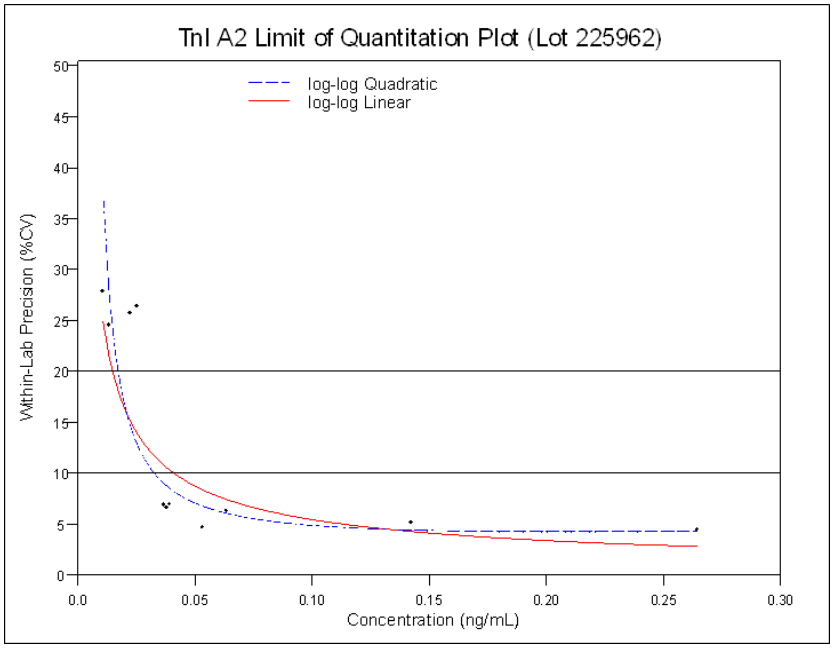


Table 13-2: Plasma LoQ Summary by Run Temperature

	18°C Run Temp			23°C Run Temp			28°C Run Temp		
Sample Pool Identification	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**
Sample 001	0.016	0.003	18.8%	0.009	0.002	21.3%	0.009	0.004	39.6%
Sample 002	0.019	0.002	12.1%	0.013	0.003	20.9%	0.012	0.006	50.1%
Sample 003	0.025	0.002	9.0%	0.023	0.004	16.8%	0.020	0.008	41.5%
Sample 004	0.027	0.002	9.1%	0.026	0.004	16.4%	0.026	0.008	29.5%
Sample 011	0.034	0.003	8.2%	0.035	0.002	6.5%	0.038	0.003	7.0%
Sample 005	0.036	0.002	6.1%	0.036	0.002	5.4%	0.038	0.003	6.7%
Sample 006	0.037	0.002	6.3%	0.037	0.002	5.7%	0.039	0.003	7.1%
Sample 007	0.055	0.003	5.1%	0.052	0.002	4.1%	0.052	0.003	5.2%
Sample 008	0.068	0.005	6.7%	0.060	0.003	4.5%	0.061	0.004	6.1%
Sample 009	0.143	0.007	4.6%	0.134	0.005	4.1%	0.137	0.007	4.9%
Sample 010	0.245	0.007	2.8%	0.252	0.008	3.2%	0.264	0.011	4.3%

Figure 13-3: Power Function Model Fits for Run Temperature at 18°C

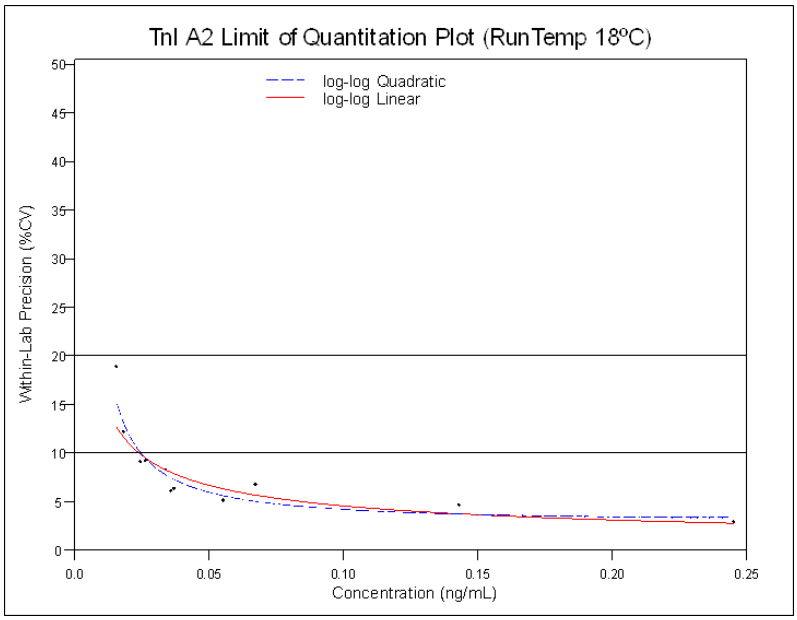
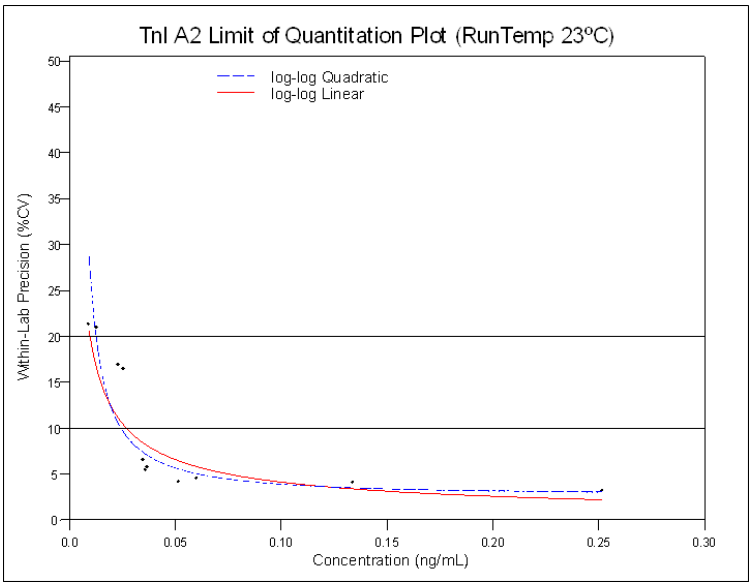


Figure 13-4: Power Function Model Fits for Run Temperature at 23°C



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Figure 13-5: Power Function Model Fits for Run Temperature at 28°C

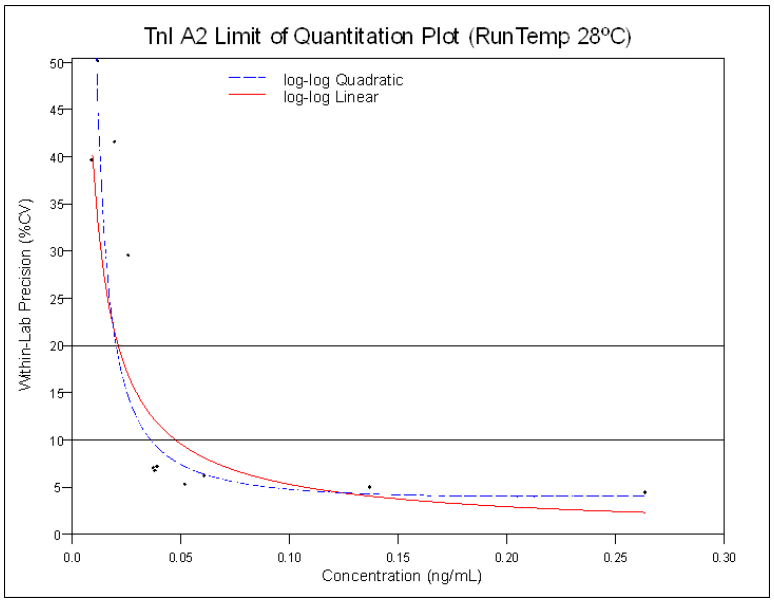


Table 13-3: Plasma LoQ Summary by Instrument

	Instrument 402603			Instrument 502884			Instrument 507310		
Sample Pool Identification	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**
Sample 001	0.011	0.003	27.8%	0.013	0.003	25.7%	0.011	0.003	23.7%
Sample 002	0.014	0.003	24.5%	0.016	0.005	30.9%	0.014	0.004	25.6%
Sample 003	0.023	0.006	25.7%	0.023	0.005	20.4%	0.022	0.006	25.5%
Sample 004	0.025	0.007	26.4%	0.027	0.005	17.7%	0.026	0.004	14.8%
Sample 011	0.037	0.003	6.9%	0.035	0.003	8.0%	0.034	0.002	6.7%
Sample 005	0.038	0.003	6.6%	0.037	0.002	5.9%	0.036	0.002	5.8%
Sample 006	0.039	0.003	6.9%	0.037	0.002	6.3%	0.037	0.002	6.0%
Sample 007	0.053	0.002	4.7%	0.053	0.002	4.2%	0.053	0.003	5.5%
Sample 008	0.064	0.004	6.3%	0.062	0.004	5.9%	0.063	0.003	5.5%
Sample 009	0.142	0.007	5.2%	0.134	0.007	5.0%	0.138	0.004	3.3%
Sample 010	0.264	0.012	4.4%	0.247	0.006	2.5%	0.250	0.008	3.4%

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Figure 13-6: Power Function Model Fits for Instrument 402603

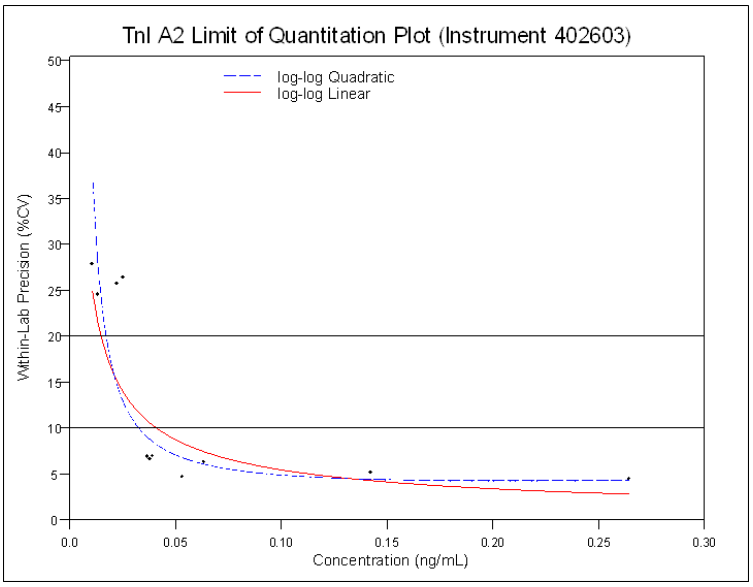


Figure 13-7: Power Function Model Fits for Instrument 502884

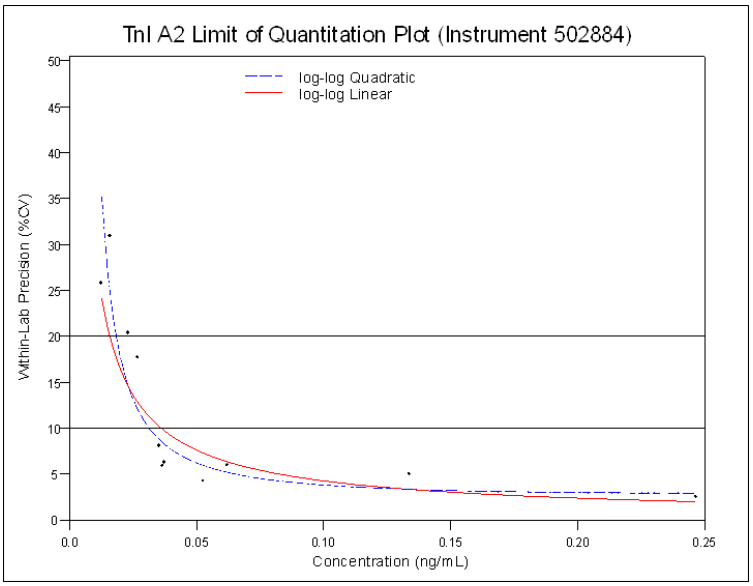


Figure 13-8: Power Function Model Fits for Instrument 507310

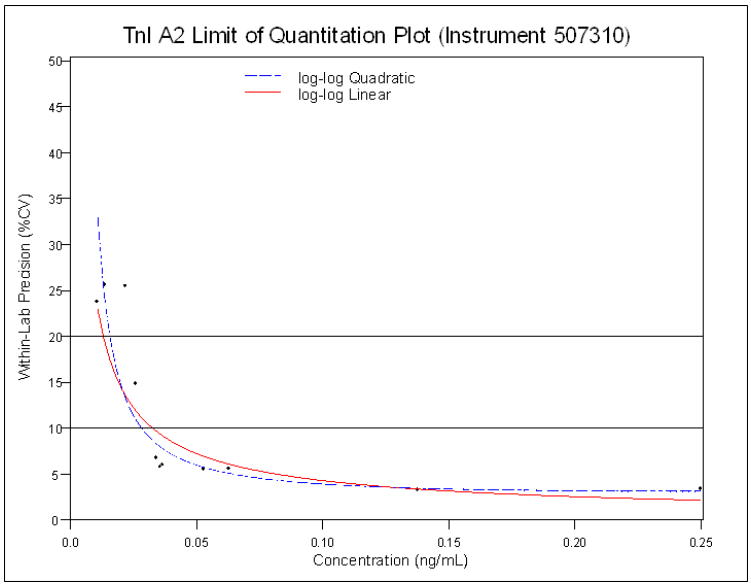


Table 13-4: Plasma LoQ Summary by Power Function Model

Group	Log-log Linear			Log-log Quadratic		
	10% CV LoQ	20% CV LoQ	Adj R^2	10% CV LoQ	20% CV LoQ	Adj R^2
Run T = 18 ºC	0.024	<0.016	0.82	0.025	<0.016	0.85
Run T = 23 ºC	0.027	0.010	0.74	0.024	0.012	0.79
Run T = 28 ºC	0.047	0.021	0.69	0.036	0.020	0.78
Lot 225961	0.035	0.015	0.77	0.030	0.017	0.84
Lot 225962	0.041	0.015	0.65	0.033	0.017	0.73
Inst 402603	0.041	0.015	0.65	0.033	0.017	0.73
Inst 502884	0.036	0.016	0.76	0.031	0.018	0.82
Inst 507310	0.033	0.013	0.76	0.028	0.016	0.83

In all cases, the quadratic power function model represents a superior fit of the lithium heparin plasma data. Therefore, BEC used the quadratic function data to derive the best estimate of LoQ.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Serum LoQ Estimate Analyses:

The same analysis was also performed for the serum LoQ study. Summary data by reagent lot is provided in **Table 13-5** and **Figure 13-9** and **Figure 13-10**. Summary data by run temperature is provided in **Table 13-6** and **Figure 13-11**, **Figure 13-12**, and **Figure 13-13**. Summary data by instrument is provided in **Table 13-7** and **Figure 13-14**, **Figure 13-15**, and **Figure 13-16**. Finally, a summary of all calculated serum 10% CV and 20% CV LoQ results are provided in **Table 13-8**.

Table 13-5: Serum LoQ Summary by Reagent Lot

	Reagent Lot 225961			Reagent Lot 225962		
Sample Pool Identification	Mean (ng/mL)	SD_{WL} (ng/mL)	CV (%)	Mean (ng/mL)	SD_{WL} (ng/mL)	CV (%)
Sample 002	0.012	0.003	29.5%	0.019	0.004	22.2%
Sample 003	0.029	0.004	12.0%	0.036	0.002	6.1%
Sample 004	0.031	0.003	8.7%	0.038	0.002	5.4%
Sample 009	0.032	0.003	8.7%	0.039	0.003	6.6%
Sample 010	0.038	0.003	7.2%	0.044	0.002	5.4%
Sample 005	0.043	0.002	5.2%	0.049	0.002	5.1%
Sample 006	0.068	0.003	4.0%	0.077	0.004	4.9%
Sample 007	0.112	0.005	4.1%	0.126	0.004	3.5%
Sample 008	0.213	0.007	3.2%	0.234	0.008	3.3%

Figure 13-9: Power Function Model Fits for Reagent Lot 225961

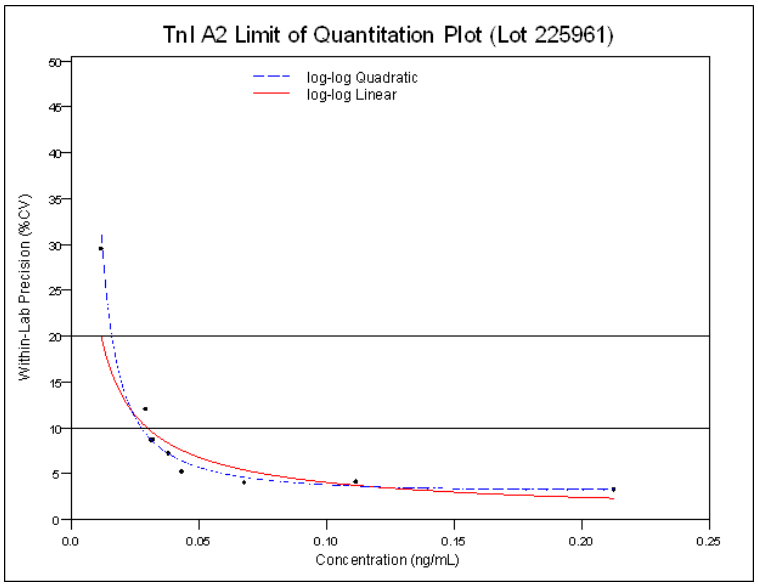


Figure 13-10: Power Function Model Fits for Reagent Lot 225962

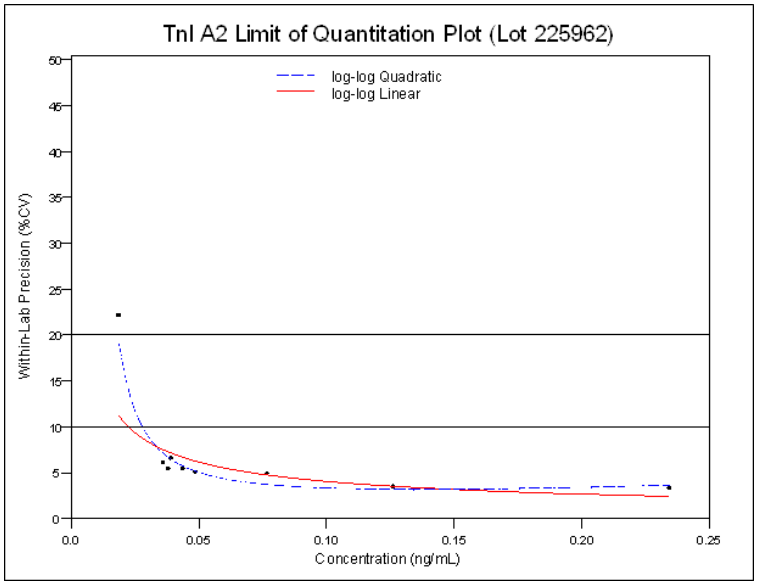


Table 13-6: Serum LoQ Summary by Run Temperature

	18 °C Run Temp			23 °C Run Temp			28 °C Run Temp		
Sample Pool Identification	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**
Sample 002	0.017	0.002	14.2%	0.017	0.005	27.1%	0.009	0.004	44.7%
Sample 003	0.030	0.002	7.6%	0.034	0.002	5.2%	0.031	0.005	15.0%
Sample 004	0.033	0.002	6.9%	0.036	0.002	5.3%	0.032	0.003	10.0%
Sample 009	0.034	0.002	6.5%	0.036	0.002	5.0%	0.033	0.004	11.2%
Sample 010	0.039	0.002	4.7%	0.041	0.002	4.7%	0.040	0.004	9.2%
Sample 005	0.045	0.002	5.2%	0.045	0.002	4.0%	0.045	0.003	6.0%
Sample 006	0.076	0.003	3.4%	0.073	0.003	4.4%	0.063	0.003	5.4%
Sample 007	0.120	0.004	3.7%	0.117	0.004	3.8%	0.112	0.005	4.2%
Sample 008	0.225	0.006	2.4%	0.222	0.007	3.2%	0.212	0.009	4.0%

Figure 13-11: Power Function Model Fits for Run Temperature 18°C

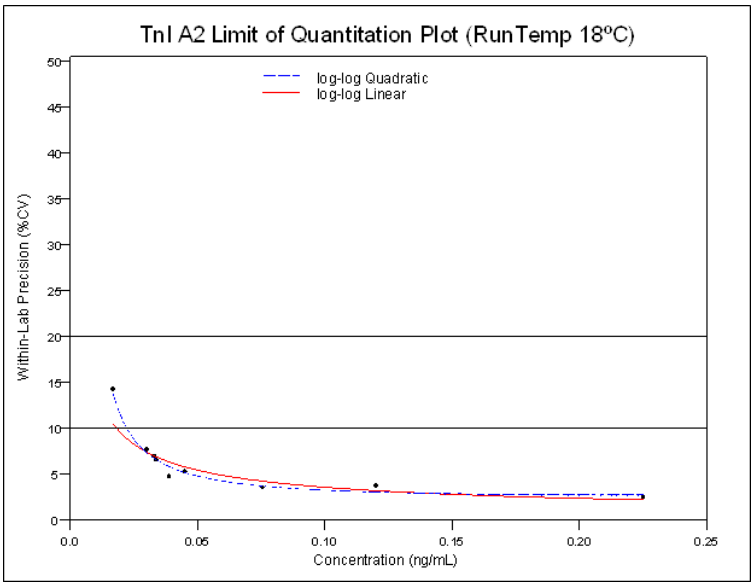


Figure 13-12: Power Function Model Fits for Run Temperature 23°C

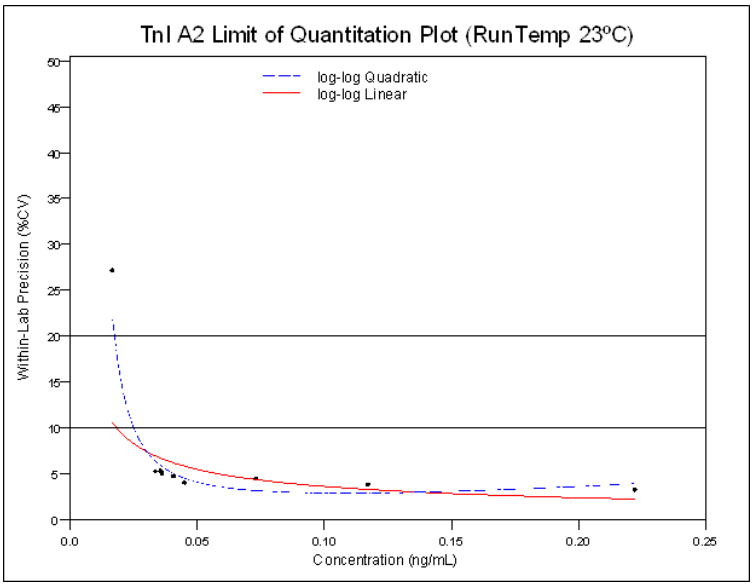


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Figure 13-13: Power Function Model Fits for Run Temperature 28°C

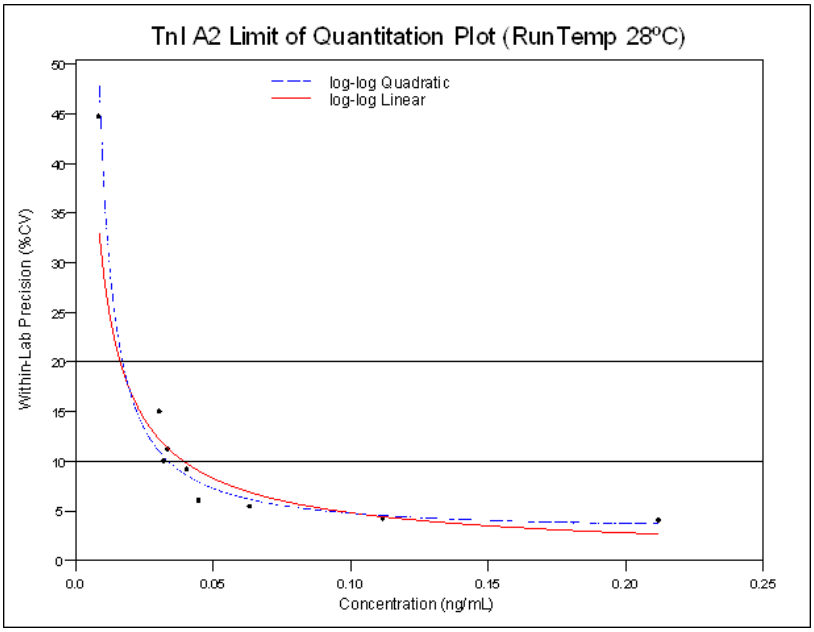

Table 13-7: Serum LoQ Summary by Instrument

	Instrument 402603			Instrument 502884			Instrument 507310		
Sample Pool Identification	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**	**Mean (ng/mL)**	**SD_{WL} (ng/mL)**	**CV (%)**
Sample 002	0.019	0.004	22.2%	0.014	0.004	30.5%	0.010	0.003	26.2%
Sample 003	0.036	0.002	6.1%	0.032	0.004	12.0%	0.026	0.003	11.9%
Sample 004	0.038	0.002	5.4%	0.035	0.003	8.9%	0.028	0.002	8.2%
Sample 009	0.039	0.003	6.6%	0.036	0.003	7.4%	0.029	0.003	10.2%
Sample 010	0.044	0.002	5.4%	0.040	0.002	6.0%	0.036	0.003	8.4%
Sample 005	0.049	0.002	5.1%	0.045	0.003	5.7%	0.042	0.002	4.5%
Sample 006	0.077	0.004	4.9%	0.069	0.003	4.2%	0.067	0.003	3.9%
Sample 007	0.126	0.004	3.5%	0.114	0.005	4.4%	0.109	0.004	3.8%
Sample 008	0.234	0.008	3.3%	0.214	0.007	3.5%	0.211	0.006	3.0%

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Figure 13-14: Power Function Model Fits for Instrument 402603

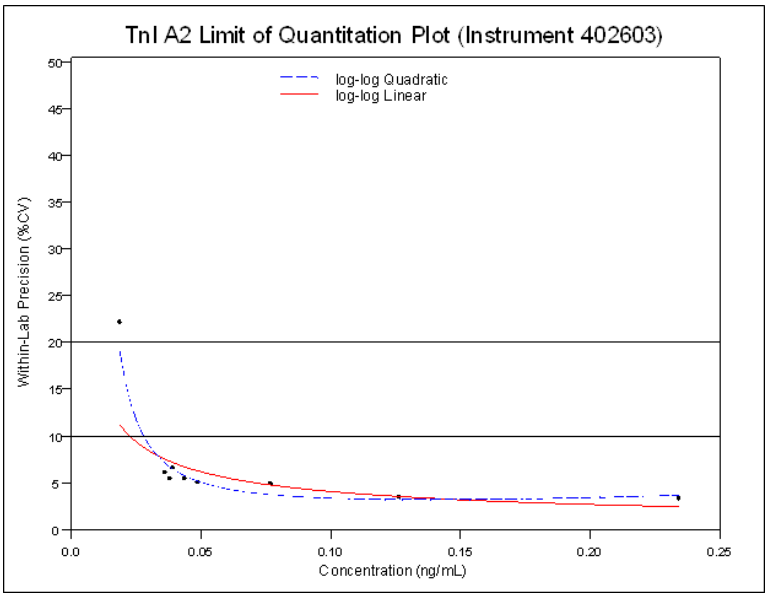

Figure 13-15: Power Function Model Fits for Instrument 502884

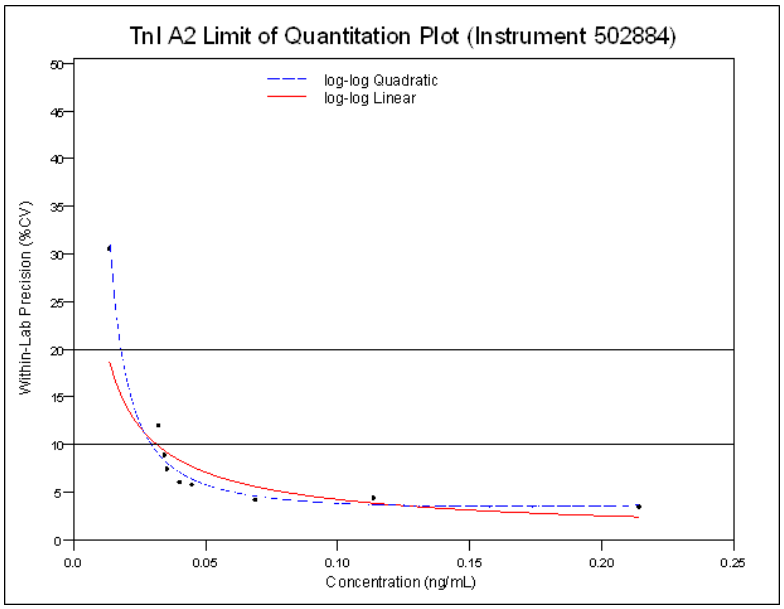

Figure 13-16: Power Function Model Fits for Instrument 507310

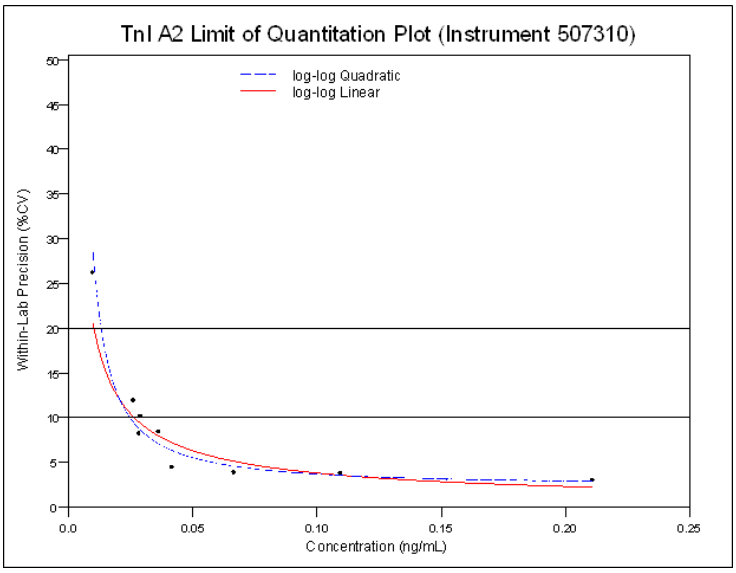

Table 13-8: Serum LoQ Summary by Power Function Model

Group	Log-log Linear			Log-log Quadratic		
	10% CV LoQ	20% CV LoQ	Adj R^2	10% CV LoQ	20% CV LoQ	Adj R^2
Run T = 18 ºC	0.018	<0.017	0.86	0.022	<0.017	0.94
Run T = 23 ºC	0.018	<0.017	0.47	0.025	0.017	0.85
Run T = 28 ºC	0.039	0.016	0.86	0.034	0.017	0.93
Lot 225961	0.030	0.012	0.82	0.027	0.016	0.95
Lot 225962	0.022	<0.019	0.63	0.028	<0.019	0.90
Inst 402603	0.022	<0.019	0.63	0.028	<0.019	0.90
Inst 502884	0.032	<0.014	0.76	0.029	0.018	0.93
Inst 507310	0.026	0.010	0.85	0.025	0.013	0.90

In all cases, the log-log quadratic power function model represents a superior fit of the serum plasma data. Therefore, BEC used the quadratic function data to derive the best estimate of LoQ.

Conclusion:

Using the best fit log-log quadratic power function for each sub-analysis, the highest estimated LoQ was chosen for the device claim. This data analysis supports a 10% CV LoQ of 0.04 ng/mL and a 20% CV LoQ of 0.02 ng/mL for both sample matrices. A copy of the revised Instructions for Use (IFU) is attached in Appendix 8.

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(13)(b) Please also provide all of the electronic data for your latest LoQ studies as Excel files including and identifying all of the variables included in your dataset (i.e., sample number, instrument number, reagent lot, calibration temperature, run temperature, run number, day number, and any other variable). Please refer to the following link which provides explanatory details on presentation format and documentation recommendations: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm

BEC Response to Question 13(b)

The latest LoQ study data is provided in an Excel file identifying all variables included in the dataset. Line data for this study is provided in STATISTICAL DATA/k121214-S001 Line Data.zip, Tab "Q2 Lmts of Detection (LoD-LoQ).

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Appendix 1: Acceptance Criteria Table

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Table A1-1 below indicates the acceptance criteria that were in place when the study was originally conducted, and if they were changed, the revised acceptance criteria. If a study was repeated or reanalyzed after the acceptance criteria were changed, only the new criteria were applied. If a study was not repeated or reanalyzed after the acceptance criteria were changed, the data were examined, and confirmed to meet the revised acceptance criteria.

Table A1-1: Summary of Analytical Studies and Acceptance Criteria

Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
Original AccuTnI+3 510(k) Submission			
1	K121214 Submission Section 8.1 – Limit of Blank	LoB ≤ 0.010 ng/mL	No change
2	K121214 Submission Section 8.2 – Limit of Detection	LoD ≤ 0.030 ng/mL Between temperature variability: for doses ≤ 0.105 ng/mL, SD ≤ 0.0084 ng/mL	LoD ≤ 0.030 ng/mL Between temperature variability: for doses ≤ 0.075 ng/mL, SD ≤ 0.006 ng/mL
3	K121214 Submission, Section 8.3 - Limit of Quantitation multi-temp and cross-temp analyses	10% CV LoQ ≤ 0.06 ng/mL 20% CV LoQ ≤ 0.03 ng/mL Between temperature variability: for doses ≤ 0.105 ng/mL, SD ≤ 0.0084 ng/mL; for doses > 0.105, CV ≤ 8%	10% CV LoQ ≤ 0.06 ng/mL 20% CV LoQ ≤ 0.03 ng/mL Between temperature variability: for doses ≤ 0.075 ng/mL, SD ≤ 0.006 ng/mL; for doses > 0.075 ng/mL, CV ≤ 8%
4	K121214 Submission, Section 8.4 - Precision	Total imprecision: For doses > 0.105 ng/mL, %CV ≤ 8%; for doses ≤ 0.105 ng/mL, SD ≤ 0.0084 ng/mL	Total imprecision: For doses > 0.075 ng/mL, %CV ≤ 8%; For doses ≤ 0.075 ng/mL, SD ≤ 0.006 ng/mL
5	K121214 Submission, Section 8.5 - Linearity	If the higher order term of the polynomial fit is significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias (maximum deviation from linearity) ≤16% for doses >0.105 ng/mL or ≤0.0168 ng/mL for doses ≤0.105 ng/ mL in comparison to the linear regression fit.	If the higher order term of the polynomial fit is significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias (maximum deviation from linearity) ≤16% for doses >0.075 ng/mL or ≤0.012 ng/mL for doses ≤0.075 ng/ mL in comparison to the linear regression fit.
6	K121214 Submission, Section 8.6- High dose Hook Effect	No hook effect from S5 calibrator concentration up to at least 2,000 ng/mL	No change

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
7	K121214 Submission, Section 8.7.1 – Reagent pack real time stability	Stable ≥ 6 months • For each time point tested, individual controls may be greater than ± 2.00 Z from their stated mean as long as that individual control is within ± 1.00Z from baseline. • The overall mean Z of control sets cannot be greater than ±1.00 Z from the baseline overall mean Z. • All replicates of normal patient samples must be ≤0.04 ng/mL on each instrument at each time point.	Stable ≥ 6 months For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 16% (2 SD) of the y-axis value of the regression line at baseline (time 0). • All replicates of normal patient samples must be ≤0.02 ng/mL on each instrument at each time point.

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
8	K121214 Submission, Section 8.7.2 – Reagent open pack stability	Stable ≥ 35 days Best fit line through all controls and time points at maximum time point (≥ 35 days) must be within ±10.0% of line fit at baseline for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ±125% of the expected SD (0.0084 ng/mL) specification will be applied.	Stable ≥ 35 days For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 10% (1.25 x 8%) of the y-axis value of the regression line at baseline (time 0).

Questions? Contact FDA/CDRH/OCE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
9	K121214 Submission, Section 8.7.3 – Stored calibration curve stability	Stable ≥ 35 days Best fit line through all controls and time points at maximum time point (≥ 35 days) must be within ±10.0% of line fit at baseline for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ±125% of the expected SD (0.0084 ng/mL) specification will be applied.	Stable ≥ 35 days For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 10% (1.25 x 8%) of the y-axis value of the regression line at baseline (time 0).

Questions? Contact FDA/CDRH/OCE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
10	K121214 Submission, Section 8.7.4 – Calibrator real time Stability	Stable ≥ 6 months • For each time point tested, individual controls may be greater than ± 2.00 Z from their stated mean as long as that individual control is within ±1.00Z from baseline • The overall mean Z of control sets cannot be greater than ±1.00 Z from the baseline overall mean Z • For primary reference calibrators, the mean % dose difference from baseline needs to be ±11% for levels S1 and S2, and ±10% for levels S3 through S5. • All replicates of normal patient samples must be ≤0.04 ng/mL on each instrument at each time point	Stable ≥ 6 months For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 16% (2 SD) of the y-axis value of the regression line at baseline (time 0). • For primary reference calibrators, the mean % dose difference from baseline needs to be ±11% for levels S1 and S2, and ±10% for levels S3 through S5. • All replicates of normal patient samples must be ≤0.02 ng/mL on each instrument at each time point

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
11	K121214 Submission, Section 8.7.5 – Calibrator open vial stability	Stable ≥ 60 days Best fit line through all controls and time points at maximum time point (≥ 60 days) must be within ±10.0% of line fit at baseline for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ±125% of the expected SD (0.0084 ng/mL) specification will be applied.	Stable ≥ 60 days For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 10% (1.25 x 8%) of the y-axis value of the regression line at baseline (time 0).
12	K121214 Submission, Section 8.8 – Interference and Analytical Specificity	For doses > 0.105 ng/mL, the percent change must be ≤ 10.0% from the diluent control. For normal samples, either the test sample must read less than or equal to the established 99th percentile URL; or, if the test samples exceed the 99th percentile URL, the difference between the test and control sample must be ≤0.01 ng/mL.	For doses > 0.105 ng/mL, the percent change must be ≤ 10.0% from the diluent control. For samples containing analyte at doses ≤ 0.075 ng/mL the change must be ≤ 0.006 ng/mL from diluent control.
13	K121214 Submission, Section 8.9 – Cross-reactivity	Cross reactivity ≤ 1.00 %	No change
14	K121214 Submission, Section 8.10 – Sample Matrix Comparison	Slope = 1.00 ± 0.10; r > 0.95	No change
15	K121214 Submission, Section 8.12 Thermal Sensitivity-Robustness	p > 0.05 or slope ≤ 0.010	No change

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
16	K121214 Submission, Section 8.13- Thermal Sensitivity – Impact on Low Dose Concordance/ Agreement	McNemar p-value non-significant (p> 0.05). If significant, concordance must be ≥ 90%; bias ≤ 0.0084 ng/mL at cutoffs.	McNemar p-value non-significant (p > 0.05). If significant, concordance must be ≥ 90%; bias ≤ 0.006 ng/mL at cutoffs. If R^2 < 0.95, then the bias estimate at the clinical cutoff of 0.03 ng/mL must be ≤0.006 ng/mL, using a best fit regression line.
17	K121214 Submission, Section 8.14 – Thermal Sensitivity- Impact on Cross-Temperature Method Comparison	Slope = 1.00 ± 0.10; r> 0.95	No change
First AI Letter Response			
18	First AI Letter, Question 1 - Concordance Repeat Study	At the URL of 0.02 ng/mL and the clinical cutoff of 0.03 ng/mL, the McNemar p-value non-significant (p> 0.05). If significant, concordance must be ≥ 90%; bias ≤ 0.0084 ng/mL at cutoffs.	McNemar p-value non-significant (p > 0.05). If significant, concordance must be ≥ 90%; bias ≤ 0.006 ng/mL at cutoffs. If R^2 < 0.95, then the bias estimate at the clinical cutoff of 0.03 ng/mL must be ≤0.006 ng/mL, using a best fit regression line.
19	First AI Letter, Question 6 – Full-Range Linearity Repeat Study	The higher order (2nd or 3rd) term of the polynomial fit should be non-significant (p > 0.05). If significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias ≤16% for doses > 0.105 ng/mL or ≤ 0.0168 ng/mL for doses ≤ 0.105 ng/mL in comparison to the linear regression fit.	The higher order (2nd or 3rd) term of the polynomial fit should be non-significant. If significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias ≤ 16% for doses > 0.075 ng/mL or ≤ 0.012 ng/mL for doses ≤ 0.075 ng/mL in comparison to the linear regression fit.
20	First AI Letter, Question 8 - Additional Interfering Substance Testing at 0.05 ng/mL troponin	The change must be ≤ 0.0084 ng/mL from diluent control for samples containing analyte at doses ≤ 0.105 ng/mL.	The change must be ≤ 0.006 ng/mL from diluent control for samples containing analyte at doses ≤ 0.075 ng/mL.
21	First AI Letter, Question 10 - Additional multi-temp precision testing	For doses > 0.105 ng/mL, %CV ≤ 8%; for doses ≤ 0.105 ng/mL, SD ≤ 0.0084 ng/mL	For doses > 0.075 ng/mL, %CV ≤ 8%; for doses ≤ 0.075 ng/mL, SD ≤ 0.006 ng/mL

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
Second AI Letter			
22	Second AI Letter, Question 3 - Truncated Range Linearity Study	N/A *Note: this new study was run after the acceptance criteria were tightened – hence no "original" specification.*	If the higher order term of the polynomial fit is significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias (maximum deviation from linearity) ≤ 16% for doses > 0.075 ng/mL or ≤ 0.012 ng/mL for doses ≤ 0.075 ng/mL in comparison to the linear regression fit.
23	Second AI Letter, Question 3 – Additional cross-temp full-range linearity analyses	If the higher order term of the polynomial fit is significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias ≤16% for doses > 0.105 ng/mL or ≤ 0.0168 ng/mL for doses ≤ 0.105 ng/mL in comparison to the linear regression fit.	If the higher order term of the polynomial fit is significant, the fit of the polynomial regression demonstrating significance at each sample must have a bias ≤16% for doses > 0.075 ng/mL or ≤ 0.012 ng/mL for doses ≤ 0.075 ng/mL in comparison to the linear regression fit.
24	Second AI Letter, Question 4 - Additional Overall precision analyses	For doses > 0.105 ng/mL, %CV ≤ 8%; for doses ≤ 0.105 ng/mL, SD ≤ 0.0084 ng/mL	For doses > 0.075 ng/mL, %CV ≤ 8%; for doses ≤ 0.075 ng/mL, SD ≤ 0.006 ng/mL
25	Second AI Letter, Question 9 - Reanalysis of In-Use Stability Studies (open reagent pack, stored calibration curve, and open calibrator vial)	Best fit line through all controls and time points at maximum time point (≥ 35 days) must be within ±10.0% of line fit at baseline for samples > 0.105 ng/mL. For samples ≤ 0.105 ng/mL, a ±125% of the expected SD (0.0084 ng/mL) specification will be applied.	For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For <u>individual</u> samples ≤ 0.075 ng/mL, the y-axis value of the regression line through all <u>replicates</u> and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through all replicates and all time points must at all times be within 10% (1.25 x 8%) of the y-axis value of the regression line at baseline (time 0).

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Study #	Study Identifier	Original Acceptance Criteria	Updated Acceptance Criteria
26	Second AI Letter, Question 9 Reanalysis of Real Time Stability Studies (reagent pack and calibrator)	• For each time point tested, individual controls may be greater than ± 2.00 Z from their stated mean as long as that individual control is within ± 1.00 Z from baseline • The overall mean Z of control sets cannot be greater than ±1.00 Z from the baseline overall mean Z • All replicates of normal patient samples must be ≤ 0.04 ng/mL on each instrument at each time point	For each sample, plot percent difference, or difference in concentration from the baseline, on the y-axis as a function of time (x-axis). Construct a linear regression through all data points. Then: • For individual samples ≤ 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 0.0075 ng/mL (1.25 x 0.006 ng/mL) of the y-axis value of the regression line at baseline (time 0). • For individual samples > 0.075 ng/mL, the y-axis value of the regression line through <u>all replicates</u> and all time points must at all times be within 16% (2 SD) of the y-axis value of the regression line at baseline (time 0). • All replicates of normal patient samples must be ≤ 0.02 ng/mL on each instrument at each time point
27	Second AI Letter, Question 10 - Calibrator Value Assignment Verification	For doses ≤ 0.105 ng/mL, the lower and upper 95% confidence limits around the mean difference between TEST and REF results must be between -0.0084 ng/mL and +0.0084 ng/mL. For doses > 0.105 ng/mL, the lower and upper 95% confidence limits around the mean difference between TEST and REF results must be within ±8% of the REF result.	For doses ≤ 0.075 ng/mL, the lower and upper 95% confidence limits around the mean difference between TEST and REF results must be between -0.006 ng/mL and +0.006 ng/mL. For doses > 0.075 ng/mL, the lower and upper 95% confidence limits around the mean difference between TEST and REF results must be within ±8% of the REF result.

Questions? Contact FDA/CDRH/OCE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-3148

Appendix 2: Original AccuTnI Fresh vs. Frozen Data
(Data originally submitted as part of k010429)

Frozen vs. Fresh Sample Comparison

Purpose: Evaluate the effect of freezing on cardiac troponin I (c TnI) levels in lithium heparin (LiHep) plasma.

Protocol: To determine regression statistics for fresh and frozen specimens, fresh lithium heparin samples were analyzed in duplicate. The frozen aliquots were stored at -20 °C or colder for a minimum of 3 days. Samples were thawed for a maximum of 1 hour, mixed, centrifuged and analyzed in duplicate.

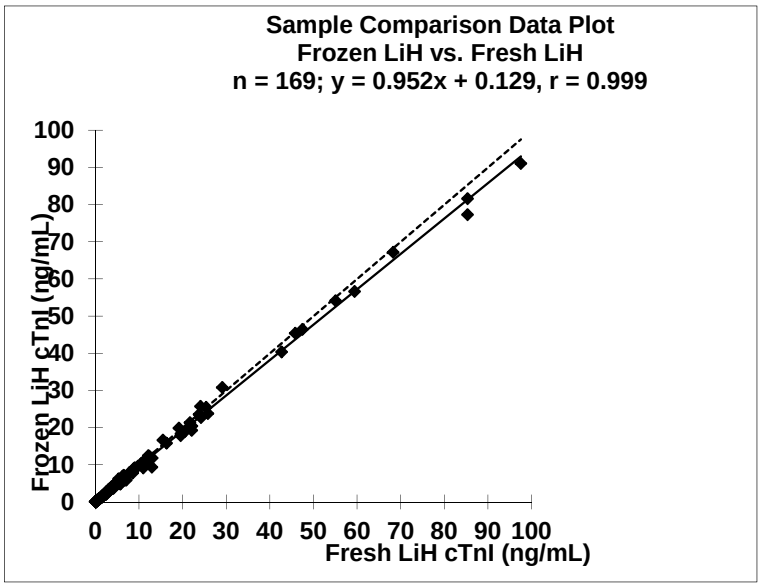
Statistical Treatment: To estimate the regression equation, a Standardized Principle Component method (a Deming method) was utilized. The correlation statistics were calculated and are shown below.

Conclusions: There were no trends noted and no clinically significant bias between fresh and frozen samples. The results are presented below in Table A2-1 and Figure A2-1.

Table A2-1: Frozen vs. Fresh Sample Comparison

n	Range of Observations (ng/mL)	Slope (95% CI of Slope)	Intercept (95% CI of Intercept)	r
169	0.02 – 91.08	0.952 (0.945 to 0.959)	0.129 (0.074 to 0.184)	0.999

Figure A2-1: Sample Comparison
Frozen Lithium Heparin vs. Fresh Lithium Heparin



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Appendix 3: AccuTnI Fresh vs. Frozen Sample Comparison (2009)

Protocol: The objective of this study was to evaluate the effect of freezing on cardiac troponin I (c TnI) levels in lithium heparin (LiHep) plasma as determined by the modified AccuTnI assay an Access 2 Immunoassay analyzer. Fresh lithium heparin samples were analyzed in singleton using one lot of AccuTnI reagent. The frozen aliquots were stored at -20 °C or colder for a minimum of 48 hours. Samples were thawed for a maximum of one hour, mixed, centrifuged and analyzed in singleton.

Statistical analysis: Both Deming and Passing-Bablok method comparisons were performed between fresh and frozen samples. Only samples with dose value > 0.01 ng/mL (analytical sensitivity) were included in the method comparison analysis. Correlation coefficient was calculated for each comparison.

Acceptance criteria: Slope = 1.00 ± 0.10

Conclusions: The slopes of both regressions between fresh and frozen samples meet the acceptance criteria. The results are presented below in Table A3-1, Table A3-2, and Table A3-3.

Table A3-1: Fresh vs. Frozen Description Summary

n	Dose Range ng/mL	r	R^2
45	(0.021 - 39.22)	1.000	1.00

Table A3-2: Passing-Bablok Method Comparison – Fresh vs. Frozen Samples

n	Intercept	95% CI of Intercept	Slope	95% CI of Slope
45	-0.0031	(-0.0048, -0.0002)	0.94	(0.93, 0.95)

Table A3-3: Deming Method Comparison – Fresh vs. Frozen Samples

n	Intercept	95% CI of Intercept	Slope	95% CI of Slope
45	-0.0093	(-0.050, 0.031)	0.94	(0.92, 0.96)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 4: Indications for Use Form

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Questions? Contact FDA/CDRH/OCE/DIDI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Indications for Use Form

510(k) Number (if known): k121214

Device Name: Access AccuTnI+3 Reagent and Calibrator for use on the Access 2 Immunoassay Systems

Indications for Use:

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Devices and Radiological Health (OIR)

_____
Division Sign-Off
Office of In Vitro Devices and Radiologic Health
Evaluation and Safety
510(k)_____

Questions? Contact FDA/CDRH/OCE/DIDSI-CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 5: 510(k) Summary

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Questions? Contact FDA/CDRH/OCE/DIDM/CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92

The assigned 510(k) number is k121214

Submitted By:

Beckman Coulter, Inc.
1000 Lake Hazeltine Drive
Chaska, MN 55318
Telephone: (952) 368-1142
Fax: (952) 368-7610

Contact Person:

Kerrie Oetter
1000 Lake Hazeltine Drive
Chaska, MN 55318
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Date Prepared:

May 24, 2013

Device Name:

Proprietary / Trade Name: Access AccuTnI+3 Reagent and Calibrator for use on the Access 2 Immunoassay Systems
Common Name: Troponin I Enzyme Immunoassay
Classification Name: Immunoassay, Troponin Subunits
Classification Regulation: 21 CFR 862.1215
Classification Product Code: MMI
Subsequent Product Code: JIT

Proprietary / Trade Name: Access 2 Immunoassay System
Common Name: Discrete photometric chemistry analyzer for clinical use
Classification Name: Discrete photometric chemistry analyzer for clinical use
Classification Regulation: 21 CFR 862.2160
Classification Product Code: JJE

Predicate Devices:

The Access AccuTnI+3 assay and calibrators claim substantial equivalence to the TnI-Ultra™ Assay and Calibrators for the Siemens ADVIA Centaur® System, FDA 510(k) Number K053020, cleared December 30, 2005.

The Access 2 Immunoassay System claims substantial equivalence to the Access 2 Immunoassay System (K922823/A007), cleared July 2, 2001.

Questions? Contact FDA/CDRH/OCE/DIDP/CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Device Description:

The Access AccuTnI+3 reagents, AccuTnI+3 calibrators and the Access 2 Immunoassay System compose the Access Immunoassay System for the quantitative determination of cardiac troponin I (cTnI) in human serum and plasma.

The Access AccuTnI+3 reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, <0.1% sodium azide, and 0.1% ProClin® 300.
- 0.1N NaOH.
- TRIS buffered saline, surfactant, <0.1% sodium azide and 0.1% ProClin 300.
- Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), <0.1% sodium azide, and 0.25% ProClin 300.

The Access AccuTnI+3 Calibrator set contains multi-point calibrators for use with the Access AccuTnI+3 assay. Individual vials contain zero or approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (μg/L) of recombinant cardiac troponin I complex, respectively, in a buffered BSA matrix, with surfactant, <0.1% sodium azide, and 0.1% ProClin 300.

Intended Use:

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.

Comparison to the Predicates:

The Access AccuTnI+3 and the predicate device, ADVIA Centaur® TnI-Ultra™, were compared. The information for the predicate device was derived from the predicate device 510(k) Summary and product labeling.

Questions? Contact FDA/CDRH/OCE/DIDT/CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Similarities between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3
Intended Use	An *in vitro* diagnostic method for the quantitative measurement of cardiac TnI in serum and plasma to aid in the diagnosis of myocardial infarction.	same
Assay Principle	Chemiluminescent sandwich immunoassay	same
Test System	Automated immunoassay instrument	same
Sample Type	Serum and heparinized plasma	same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	same
Primary Reagent Materials	Solid phase magnetic particles, anti-cTnI antibodies	same

Differences between the Access AccuTnI+3 Reagent and Calibrator and the Predicate

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3
Sample Type	EDTA plasma	No EDTA plasma claim
Immunoassay Instrument	ADVIA Centaur	Access 2 Immunoassay System
Calibrator Materials	Bovine cTnI in goat serum	Recombinant troponin complex in buffered BSA
Calibrators: number and type	Two Lyophilized : high and low (use with Master Curve)	Six Liquid: approximately 0, 0.3, 1.2, 5.0, 25 and 100 ng/mL with no master curve
Specific Reagent Materials	Polyclonal goat anti-cTnI antibody labeled with acridinium ester, 2 biotinylated mouse monoclonal anti-cTnI antibodies, magnetic particles conjugated with streptavidin	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti-human cTnI
Sample Volume	100µl	55µl
Analytical Measuring Range	0.008 ng/mL to 50 ng/mL	0.02 ng/mL to 100 ng/mL
Acute Myocardial Infarction (AMI) Cutoff	0.9 ng/mL per WHO-defined cutoff	0.03ng/mL based on clinical trial outcome
Expected Results (Upper Reference Limit)	99th percentile of 0.04 ng/mL; range of 0.02- 0.06 ng/mL	99th percentile of 0.02 with a 95% Confidence Interval (CI) of 0.01- 0.05 ng/mL
Precision	Total CV of 10% at a level of 0.042 ng/mL	Total CV of ≤8% at concentrations >0.075 ng/mL. SD ≤0.006 at concentrations ≤0.075 ng/mL

Questions? Contact FDA/CDRH/OCE/DIDP/CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Characteristic	Predicate Device ADVIA Centaur® TnI-Ultra™ K053020	New Device Access AccuTnI+3
Indications for Use Statement	The ADVIA Centaur® TnI-Ultra (TnI Ultra) is for *in vitro* diagnostic use in the quantitative determination of cardiac Troponin in human serum and heparinized and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures. The ADVIA Centaur® TnI-Ultra Calibrator is for the in-vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® System.	The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction. The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

The Access 2 Immunoassay System and the previously cleared version of the Access 2 Immunoassay System were compared.

Similarities between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 System K922823/A007	New Device Access 2 System
Indication for Use	The Access 2 Immunoassay system is an *in vitro* diagnostic device used for the quantitative, semi-quantitative, or qualitative determination of various analyte concentrations found in human body fluids.	same
Operating Principle	Micro computer controlled, random and continuous access	same
Assay Type	Enzyme immunoassays	same
Detection	Chemiluminescent	same
Modules	Carousel, pipettor, analytical, fluidic, electronic/systems computer/peripheral	same

Questions? Contact FDA/CDRH/OCE/DIDP/CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Differences between the Access 2 Immunoassay System and the Predicate

Characteristic	Predicate Device Access 2 Immunoassay System K922823/A007	New Device Access 2 Immunoassay System
Thermal algorithm capability	Not present	Present
Assay Protocol File (APF)	AccuTnI APF	AccuTnI APF with addition of the thermal algorithm and "U" command
Software	Version 2.4-3.2	Version 3.3: added capability to implement the thermal algorithm and "U" Command; added result suppression when instrument internal case temperature is outside 18° to 36°C
Operating Temperature	18°C to 32°C ambient	18°C to 28°C ambient 18°C to 36°C instrument case temperature

Questions? Contact FDA/CDRH/OCE/DIDP/CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Appendix 6: FDA Forms 3654

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Records processed under FOIA Request #2013-6265; Released by CDRH on 08-17-2015

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

CLSI C28-A3c, Defining Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3] # 7-224		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☒
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Department of Health and Human Services
Food and Drug Administration

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

CLSI EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#7-110	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☒
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

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[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

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STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach ; Approved Guideline

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2] ?	☒	☐
FDA Recognition number [3] # 7-193		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☒
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☒	☐
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5] ?	☒	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach ; Approved Guideline

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
4.7	Sample Preparations and Value Assignment	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
The example in the text uses 5 samples evenly spaced in concentration over the analyte range.

DESCRIPTION
Additional determinations were made with more than 5 samples, including extra samples at low concentrations.

JUSTIFICATION
FDA: "We recommend that in your new linearity study, you span your claimed range but also include several samples at the lower end of your reportable range (for example a value around your cut-off but above your LoQ and several samples under 1 ng/mL)."

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

CLSI EP07-A2, Interference Testing in Clinical Chemistry Approved Guideline

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#7-127	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☒
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☒	☐
Were there any deviations or adaptations made in the use of the standard?	☒	☐
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☒	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
CLSI EP07-A2, Interference Testing in Clinical Chemistry Approved Guideline

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7	Estimation of Interference Characteristics	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
The first option was chosen: evaluating the effects of potentially interfering substances added to the sample of interest

DESCRIPTION
The second option was not chosen: evaluating the bias of individual, representative patient specimens in comparison to a highly specific comparative measurement procedure

JUSTIFICATION
There is no reference measurement procedure for troponin with which to compare.

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3] # 7-233		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☒
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☒	☐
Were there any deviations or adaptations made in the use of the standard?	☒	☐
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☒	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

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[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

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EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE
CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
5.4	Precision Profile Approach (LoD)	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
The protocol and analysis described in this section was used rather than the "Classical Approach" from Section 5.3

DESCRIPTION
Standard deviations at multiple low concentrations were determined to create a precision profile. The concentration where 95% of results are above LoB was determined from this profile.

JUSTIFICATION
There is a relationship between standard deviation and concentration at very low concentrations due to the excellent imprecision characteristics of this assay. Therefore, this relationship must be taken into account when determining LoD.

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
6.6	Variant Approach: Combined Limits of Detection and Quantitation Evaluation	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
a) The precision profile approach was used for both LoQ and LoD (see above). b) The measure used was within-laboratory imprecision.

DESCRIPTION
All LoD and LoQ samples were combined in a study to estimate within-laboratory imprecision of each sample.

JUSTIFICATION
a) Combining LoD and LoQ samples allows for a more robust fit of a precision profile that can be used for both measurements. b) From EP17-A2: " within-laboratory precision - no associated bias goal - for cardiac troponin"

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
6.5	Data Analysis (LoQ)	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖
The worst case LoQ across all calibration temperature conditions was chosen as the LoQ for the measurement procedure.

DESCRIPTION
The statement in the guideline says the worst case value is chosen when 2 or 3 lots are used. In this case the worst case over 2 sample types and 3 calibration temperature conditions was chosen.

JUSTIFICATION
Choosing the worst case among calibration temperatures provides a similar scenario to that in the guideline but uses the variation that a laboratory may see if they calibrated and then ran per standard lab practices over multiple run temperatures.

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

CLSI EP25-A: Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3] # 7-235		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☒
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☒	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☒	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☒
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☒
Were there any deviations or adaptations made in the use of the standard?	☐	☒
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☒
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☒
Is there an FDA guidance [6] that is associated with this standard?	☐	☒
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

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Appendix 7: Official Correspondent Letter

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Questions? Contact FDA/CDRH/OCE/DHDC at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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May 09, 2013

Paula Velasco Caposino, Ph.D.
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center-W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-002

RE: 510(k) #k121214 – Official Correspondent
Access AccuTnI+3 on the Access 2 Immunoassay Systems

Dear Dr. Caposino:

The official correspondent for 510(k) #k121214 has changed from Valynda Machen to Kerrie Oetter.

If there are questions, you may contact me by telephone at (952) 368-7858, by fax at (952) 368-7610, or by e-mail at ksoetter@beckman.com.

Sincerely,

Kerrie Oetter
Senior Regulatory Affairs

Questions? Contact FDA/CDRH/OCE/DAD at CDRH-FOISTATUS@fda.hhs.gov or 301-796-9118

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Appendix 8: Device labeling (Instructions for Use, IFU)

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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3

REF A98143

FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

The troponins (I, C, and T) are members of a complex of proteins that modulate the calcium-mediated interaction between actin and myosin within muscle cells.[1] The nomenclature of these distinct proteins of the troponin complex is derived from their respective function in muscle contraction. Troponin T anchors the troponin complex to tropomyosin of the thin filament, whereas troponin I inhibits actomyosin ATPase, and troponin C is a calcium-binding subunit. Three isotypes of troponin I (TnI) have been identified: one associated with fast-twitch skeletal muscle, one with slow-twitch skeletal muscle, and one with cardiac muscle. The slow and fast-twitch isoforms have a similar molecular weight of approximately 20,000 dalton (Da) each. The cardiac-specific TnI (cTnI) isoform has a molecular weight of approximately 24,000 Da and contains a post-translational tail of 31 amino acids on the N-terminus of the molecule.[2,3] This sequence and the 42% and 45% dissimilarity with the sequences of the other two isoforms have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other non-cardiac TnI forms.[4,5] As a result of its high tissue specificity cTnI is a cardio-specific, highly sensitive marker for myocardial damage. The Access AccuTnI+3 assay uses monoclonal antibodies specifically directed against human cardiac troponin I.

In myocardial infarction (MI), cTnI levels rise in the hours after the onset of cardiac symptoms, reaching a peak at 12–16 hours and can remain elevated for 4–9 days post MI.[6,7] Numerous pathologies can potentially cause troponin elevations without overt ischemic heart disease.[8,9] These pathologies include, but are not limited to, congestive heart failure, acute and chronic trauma, electrical cardioversion, hypertension, hypotension, arrhythmias, pulmonary embolism, severe asthma, sepsis, critical illness, myocarditis, stroke, non-cardiac surgery, extreme exercise, drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms), end stage renal disease, and rhabdomyolysis with cardiac injury.[9,10] Importantly, these other etiologies rarely demonstrate the classic rising and falling pattern experienced with a MI which highlights the importance of serial monitoring when the clinical scenario is confusing.[8,11,12]

Definition of Myocardial Infarction

In 2012, a Task Force of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) published an updated redefinition of MI in which biomarkers play a central role.[12] Professional groups recognize cardiac troponin (cTn) as the preferred biomarker for MI diagnosis.

The 2012 Third Universal Definition of Myocardial Infarction document states that the following is one criterion for the diagnosis of MI:

- "Detection of a rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch

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block (LBBB);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy."[12]

Additionally, the Third Universal Definition of Myocardial Infarction document recommends an optimal imprecision level (coefficient of variation, or CV) for troponin assays ≤ 10% at the 99th percentile URL of a healthy population, and recognizes that assays with imprecision > 10% CV do not cause false positive results, but assays with CV > 20% should not be used.[12]

Because cTn may not appear in blood within the first hours after myocardial injury,[13] cTn should be measured upon admission, and then serially at regular intervals to demonstrate a rise and/or fall in cTn values. When an increased cTn value is encountered in the absence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.[14]

Principles of the Procedure

The Access AccuTnI+3 assay is a two-site immunoenzymatic ("sandwich") assay. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant-containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti-cTnI antibody are added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody - alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access AccuTnI+3 Reagent Pack (for use on Access 2 Immunoassay Systems)

Cat. No. A98143: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Paramagnetic particles coated with mouse monoclonal anti-human cardiac troponin I (cTnI) suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA) matrix, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	0.1 N NaOH.
R1c:	TRIS buffered saline, surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1d:	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, goat, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.

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- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.25% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and lithium heparin plasma are preferred samples. Matched serum and lithium heparin plasma samples were tested using the Access AccuTnI+3 assay. Regression and correlation analysis are shown below:

n	Range of Observations (ng/mL)	Intercept (95% CI)	Slope (95% CI)	Correlation Coefficient (r)
97	0.02 – 72	0.00 (-0.01 – 0.00)	1.03 (1.00 – 1.05)	0.99
43	0.02 – 0.5	0.00 (0.00 – 0.00)	0.98 (0.93 – 1.02)	0.99

   Heparin plasma and serum samples **should not be used interchangeably.**[16]

2. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] To minimize the effect of preanalytical factors, observe the following recommendations for handling, processing, and storing blood samples:
   - Collect all blood samples observing routine precautions for venipuncture.[17]
   - Allow serum samples to clot completely before centrifugation. Time to clot may be prolonged in serum samples due to the patient's clinical condition or in patients receiving anticoagulant therapy.[17]
   - Keep tubes stoppered at all times.[17]
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than two hours.
   - Samples should be centrifuged and refrigerated within two hours of blood draw.
   - Serum or plasma should be physically separated from contact with cells as soon as possible with a maximum time limit of two hours from the time of collection.
   - Remove any residual fibrin or cellular matter. Failure to do so can contribute to falsely elevated results.
   - For plasma, avoid transferring material from the white blood cell/platelet layer located just above the red blood cells. If a fixed angle rotor is used for centrifugation, care should be taken to avoid resuspending platelets.
   - Turbid serum or plasma samples containing particulate matter should be transferred from the original tube and recentrifuged prior to assay. A specimen (original tube) that contains a separating device (gel barrier) is never to be recentrifuged.
   - If the assay will not be completed within 24 hours, or for shipment of samples, freeze at -20°C or colder.[17]
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
   - Samples may be stored for six months at -20°C.
3. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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4. Thaw samples only once and centrifuge all thawed samples prior to analysis. Do not thaw in a water bath.

Materials Provided

R1 Access AccuTnI+3 Reagent Packs

Materials Required But Not Provided

1. Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
   Provided at zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (µg/L).
   Cat. No. A98144
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access 2**
   Access Wash Buffer II, Cat. No. A16792

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use fifty–five (55) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL. To change sample reporting units to the International System of Units (SI units) µg/L, or alternate units such as pg/mL or ng/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System (µg/L), multiply ng/mL by multiplication factor 1. For manual conversion to pg/mL or ng/L, multiply ng/mL by a factor of 1000.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

An active calibration curve is required for all tests. For the Access AccuTnI+3 assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[20] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since

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obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data, and the application of mathematical adjustments. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. This product is for use on Access 2 Immunoassay Systems only. It is not compatible with UniCel DxI systems.
2. For optimal performance, ambient laboratory temperature should be maintained between 18°C and 28°C (64.4°F and 82.4°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations. Up to 10% residual systematic bias may be observed when comparing patient results obtained at 18°C and 28°C (64.4°F and 82.4°F).
3. The reportable measuring range of the assay is defined as the range from 20% CV LoQ to the S5 calibrator, 0.02 to ~100 ng/mL (µg/L). The analytical range of the assay is defined as the range from LoD to the S5 calibrator, 0.01 to ~100 ng/mL (µg/L). Troponin I may be detected in samples between LoD and LoQ, but with increased imprecision. Dependent upon the concentration of Troponin I in the sample (X), report results per the description in the table below, adapted from CLSI EP17-A2.[21]

Access AccuTnI+3 Result (X) on Access 2	Report result (X) as:
X < 0.01 ng/mL (LoD)	Troponin I not detected; result < 0.01 ng/mL
0.01 ng/mL (LoD) ≤ **X** < 0.02 ng/mL (20% CV LoQ)	**X** ng/mL, interpret result with caution due to higher assay imprecision
X ≥ 0.02 ng/mL (20% CV LoQ)	**X** ng/mL
X > ~100 ng/mL (S5 calibrator value)	> ~100 ng/mL

4. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[22,23] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
5. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[24,25] Fibrinolytic agents activate proteases that may influence protein measurements, including troponin.[26] Carefully evaluate the results of patients suspected of having these types of interferences.
6. The thermal profile of native human cardiac troponin I was used in development of this assay. Troponin I not from this source (e.g. recombinant antigens) may behave differently.
7. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[17,18,19] Following blood collection tube manufacturers' specimen collection and handling recommendations are essential to reduce preanalytical errors.
8. The Access AccuTnI+3 assay is not intended to be used in isolation. Results should be interpreted in conjunction with other diagnostic tests and clinical information. When serial samples are obtained and troponin is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury.[12]
9. The Access AccuTnI+3 assay does not demonstrate any "hook" effect up to 2500 ng/mL (µg/L).

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Expected Values

Apparently Healthy Adults

Beckman Coulter conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently healthy adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. Lithium heparin plasma samples were evaluated. Five hundred twenty-seven (527) subjects were enrolled at seven geographically diverse locations. Both male and female subjects were included with approximately half above the age of 40 years and the other half between 18 and 40 years.

Subjects were excluded from the study if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system, including: hypertension, angina, coronary artery disease, history of MI, history of percutaneous transcoronary angiography/angioplasty (PTCA) or coronary artery bypass graft (CABG), peripheral artery disease including cerebrovascular disease/stroke or deep vein thrombosis, hemostatic disorders, and/or congestive heart failure.
- Currently taking a medication for cardiovascular disease, including: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, blood thinners, and/or platelet inhibitors.
- Diabetes.
- Chronic kidney disease.
- Other serious chronic disease(s), including: cancer, leukemia, emphysema, chronic obstructive pulmonary disease (COPD), HIV, HBV, HCV, lupus erythematosus, rheumatoid arthritis, and/or scleroderma.
- Acute bacterial or viral infection, including: bronchitis, upper respiratory infection, strep throat, influenza, pneumonia, mononucleosis, oral/genital herpes outbreak, and/or urinary tract infection.
- Pregnancy.

Results from this study demonstrated the 99th percentile upper reference limit (URL) to be 0.02 ng/mL (95% CI: 0.01 – 0.05).

99th Percentile Upper Reference Limit of a Healthy Population

n	Age Range (years)	99th Percentile (95% CI)
527	18–94	0.02 ng/mL (0.01–0.05)

In addition to this Reference Interval study of healthy adults, a multicenter prospective study of 1929 patients presenting to the Emergency Department with chest pain was conducted in order to evaluate diagnostic cutoff values and establish clinical utility. See the following Clinical Performance Evaluation section for further information.

Clinical Performance Evaluation

Diagnosis of Myocardial Infarction

As described in the Summary and Explanation section of this document, the Universal Definition of Myocardial Infarction document has recommended the use of more sensitive cTn assays and lower cutoffs. To establish clinical performance of Access AccuTnI+3 to aid in the diagnosis of MI, a clinical study was conducted to evaluate sensitivity (% MI correctly identified) and specificity (% non-MI correctly identified) at cutoffs near and at the 99th percentile URL.

The multicenter prospective study enrolled 1929 subjects from Emergency Department (ED) patients presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes (ACS). A total of 14 geographically diverse, primary care hospital-associated emergency departments participated, reflecting regional, urban, suburban, and rural patient populations.

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Study endpoints (final diagnoses) were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction.[11]* Investigators and adjudicators were blinded to the Access AccuTnI+3 assay results. All results presented below were based on the adjudicated diagnoses. The MI incidence was 13% (253/1929).

To assess performance of the Access AccuTnI+3 assay, study samples were tested at four independent testing facilities on an Access 2 Immunoassay System. Testing was performed using lithium heparin plasma samples.

*The 2012 Third Universal Definition of Myocardial Infarction was published after completion of this prospective study.[12]

Clinical Sensitivity and Specificity

The American College of Emergency Physicians (ACEP) recommends serial troponin measurements for patients presenting early after symptom onset (< 8 hours).[27] However, patient estimates of symptom timing may not be totally reliable, prompting serial sampling recommendations after admission to the emergency department. Based on these guidelines and literature recommendations, study results are presented for the following time intervals:

- < 8 hours and ≥ 8 hours after symptom onset
- Baseline, ≥ 1 – 3 hours, ≥ 3 – 6 hours, and ≥ 6 – 9 hours after admission

Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC) were generated for serial time intervals after symptom onset and admission. Study results showed the AccuTnI+3 assay to have significant diagnostic efficacy at all time intervals (AUCs 0.94-0.97, $p < 0.0001$).

Diagnostic sensitivity (% MI correctly diagnosed) and specificity (% Non-MI correctly diagnosed) were also determined as shown in the tables below. Cutoffs of 0.02 ng/mL and 0.03 ng/mL yielded 97% and 94% sensitivity respectively for cTnI measurements ≥ 8 hours after symptom onset. Specificity ranged from 82% to 87%.

A cutoff of 0.03 ng/mL may be used as an aid in the diagnosis of MI as this cutoff yields 94% (91-98) sensitivity, and 87% (85-89) specificity.

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Symptom Onset

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Symptom Onset	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	< 8 hours	96	94– 99	83	81 – 86
	≥ 8 hours	97	94 – 100	82	79 – 84
0.03	< 8 hours	92	87 – 96	89	87 – 91
	≥ 8 hours	94	91 – 98	87	85 – 89

Diagnostic Sensitivity and Specificity for Serial Time Intervals After Admission to the Emergency Department

TnI cutoff for Diagnosis of MI (≥) (ng/mL)	Hours After Admission to ED	Sensitivity (MI patients correctly diagnosed)		Specificity (Non-MI patients correctly diagnosed)	
		%	95% CI	%	95% CI
0.02	Baseline	92	88 – 95	84	83 –86
	≥ 1 to 3	98	94 – 100	86	83 – 88
	≥ 3 to 6	98	95 – 100	81	78 – 83
	≥ 6 to 9	93	81 – 99	76	71 – 82
0.03	Baseline	87	83 – 91	89	88 – 91
	≥ 1 to 3	96	91 – 99	89	87 – 91
	≥ 3 to 6	95	90 – 99	87	84 – 89
	≥ 6 to 9	91	78 – 97	87	82 – 91

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In clinical practice, even higher specificity is attained from detection of a rise and/or fall in cardiac biomarker values as described in the Universal Definition of Myocardial Infarction.[11,12] When serial samples are obtained and the marker is considered in the clinical context of each patient, acute events such as MI may be distinguished from other conditions causing myocardial injury. The AccuTnI+3 assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Positive Predictive Values (PPV, probability of MI diagnosis in patients with elevated cTnI) and Negative Predictive Values (NPV, probability of non-MI diagnosis in patients with non-elevated cTnI) were calculated for the multicenter prospective study, per CLSI Guideline I/LA21-A2.[28] Predictive value analysis, unlike ROC analysis, is directly proportional to the prevalence of disease in the intended use population. The overall MI prevalence of 13% in this study is consistent with literature and public health findings, and indicates that the study population is representative of the intended use population. Non-representative study populations with high MI prevalence (35-50%) may overestimate apparent diagnostic accuracy, particularly PPVs (up to 80-90%).[29] Since predictive value analysis is prevalence dependent, results will vary by region and facility.

Study results are shown in the following tables. NPVs indicate nearly all patients with cTnI values < 0.03 ng/mL were diagnosed with conditions other than myocardial infarction (non-MI). PPVs indicate that approximately 51-58% of patients with cTnI values ≥ 0.03 ng/mL were diagnosed with MI.

PPV and NPV for Serial Time Intervals After Symptom Onset

AccuTnI cutoff (ng/mL)	Hours After Symptom Onset	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	< 8 hours	49	43 – 54	99	99 – 100
	≥ 8 hours	43	38 – 48	100	99 – 100
0.03	< 8 hours	58	52 – 64	98	98 – 99
	≥ 8 hours	51	45 – 56	99	99 – 100

PPV and NPV for Serial Time Intervals After Admission to the Emergency Department

AccuTnI cutoff (ng/mL)	Hours After Admission to ED	Positive Predictive Value (Patients above cutoff diagnosed as MI)		Negative Predictive Value (Patients below cutoff diagnosed as Non-MI)	
		%	95% CI	%	95% CI
0.02	Baseline	47	43 – 51	99	98 – 99
	≥ 1 to 3	45	39 – 51	100	100 – 100
	≥ 3 to 6	46	41 – 52	100	99 – 100
	≥ 6 to 9	41	31 – 51	98	97 – 100
0.03	Baseline	55	50 – 60	98	97 – 99
	≥ 1 to 3	53	46 – 59	100	99 – 100
	≥ 3 to 6	54	49 – 60	99	98 – 100
	≥ 6 to 9	55	43 – 67	98	96 – 100

Note: Since predictive value analysis is prevalence-dependent, results will vary by region and facility.

These results are representative of the use of low troponin cutoffs, emphasizing the importance of serial samples when low cutoffs are used. However, even a single elevated troponin value increased the probability of MI from 13% to 51-58%, providing important information to the clinician.

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Non-MI patients with elevated cTnI values (Myocardial Injury)

Of the 1676 non-MI patients in the Beckman Coulter prospective multicenter pivotal trial, 217 (13%) had at least one cTnI value ≥ 0.03 ng/mL on one or more of the serial draws. Of these 217 patients, 98.6% (214/217) were found to have cardiac conditions such as angina, atrial fibrillation, cardiomyopathy, carditis, heart failure, severe coronary artery disease, tachycardia; or non-cardiac conditions such as renal failure or pulmonary embolism that may result in myocardial damage. Results are consistent with literature findings that cTnI may be elevated in non-MI patients with coronary and/or non-coronary disease with myocardial injury.[30,31] Elevated cTnI values in a non-MI patient should not be disregarded. Troponin is specific for myocardial injury; serial samples and clinical context allow identification of patients with acute and chronic conditions causing myocardial injury.

Specific Performance Characteristics

Linearity

The Access AccuTnI+3 assay demonstrates clinically acceptable linearity throughout the analytical measuring range. Twelve studies, based on CLSI EP6-A,[32] were performed to determine linearity of the Access AccuTnI+3 assay. For each study, one high sample at or above the highest calibrator level and one low sample approximately at the limit of detection were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample and eight replicates of the high sample were run on the Access 2 Immunoassay System. The Access AccuTnI+3 assay demonstrates linearity with a maximum deviation between a linear and non-linear fit of < 16% for samples > 0.075 ng/mL (μg/L), and < 0.012 ng/mL (μg/L) for samples ≤ 0.075 ng/mL (μg/L).

Imprecision

This assay exhibits total imprecision of ≤ 8% at concentrations > 0.075 ng/mL (μg/L), and total Standard Deviation (SD) ≤ 0.006 ng/mL (μg/L) at concentrations ≤ 0.075 ng/mL (μg/L). One study, based on CLSI EP5-A2[33] guidelines, provided the following data. This study used one low spiked patient pool, three commercial controls and one high patient pool. These samples were tested in duplicate in two runs per shift, two shifts per day, over a total of 13 days, generating at least 20 independent assays.

Sample	Mean (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
Low Spiked Patient Pool	0.07	5	5	7
Commercial Control 1	0.91	2	5	5
Commercial Control 2	1.96	2	5	5
Commercial Control 3	13.97	2	5	5
High Patient Pool	56.36	5	4	6

A separate study was performed to assess overall imprecision by incorporating additional variables than the study above. This overall imprecision study was conducted over 14 days and included multiple instruments, calibrations, reagent lots, and fluctuations in laboratory temperature. Three patient pools were analyzed throughout this study.

Sample	Mean (ng/mL)	Overall Imprecision (SD, ng/mL)	Overall Imprecision (%CV)
Patient pool 1	0.04	0.003	8
Patient pool 2	0.43	0.022	5
Patient pool 3	1.01	0.043	4

Analytical Specificity/Interferences

The following potential interfering substances were added to lithium heparin plasma pools at three concentrations of cTnI (0.01 ng/mL, approximately 0.05 ng/mL, and approximately 0.50 ng/mL). Additionally, each substance was tested at two concentrations. This study was run

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on five Access 2 Immunoassay Systems and values were calculated as described in CLSI EP7-A2.[34] At the highest concentrations listed below, no interference was observed.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Allopurinol	40 mg/dL
Ambroxol	40 mg/dL
Ampicillin	5 mg/dL
Ascorbic Acid	6 mg/dL
Atenolol	1 mg/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	290 ng/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Cocaine	2 mg/dL
Diclofenac	5 mg/dL
Digoxin	200 ng/mL
Dopamine	30 mg/dL
Erythromycin	20 mg/dL
Fibrinogen	1000 mg/dL

Substance	Highest Concentration Added
Furosemide	40 mg/dL
Hemoglobin	5 mg/mL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Low MW Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nifedipine	60 µg/mL
Nitrofurantoin	6.4 mg/dL
Nystatin	2.15 mg/dL
Oxytetracycline	24 mg/dL
Phenytoin	10 mg/dL
Propranolol	500 µg/mL
Quinidine	2 mg/dL
Simvastatin	20 µg/mL
Theophylline	25 mg/dL
Triglycerides	3000 mg/dL
Trimethoprim	7.5 mg/dL
Verapamil	16 mg/dL
Warfarin	30 µg/mL

To evaluate potential cross-reactivity of the assay with other myofibrillar proteins, the substances shown in the following table were added to two levels of cTnI human lithium heparin plasma samples and run on an Access 2 Immunoassay System.
Values for cross-reactivity were calculated as described in CLSI EP7-A2.[30] No significant cross-reactivity was observed (<1%).

Substance	Concentration Added (ng/mL)
Actin	1000
Cardiac troponin C	1000
Recombiant human CK-MB	1000
Myoglobin	1000
Myosin	1000
Recombinant human cTnT	250
Skeletal troponin I	1000
Tropomyosin	1000

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Limit of Blank

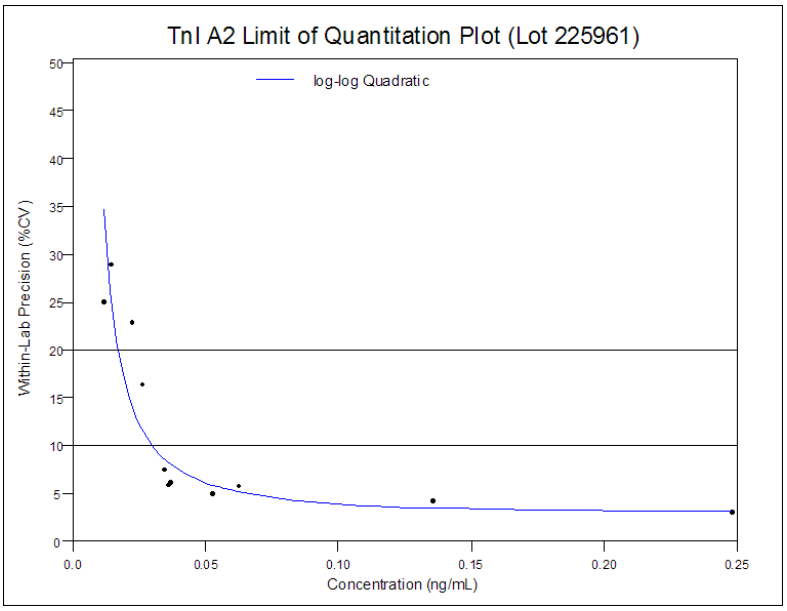
The Access AccuTnI+3 assay has a Limit of Blank (LoB) of < 0.01 ng/mL (µg/L). One study determined the LoB for Access AccuTnI+3 to be 0.003 ng/mL (µg/L). LoB was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Detection

The Access AccuTnI+3 assay has a Limit of Detection (LoD) of 0.01 ng/mL (µg/L). One study determined the LoD for Access AccuTnI+3 to be 0.008 ng/mL (µg/L). LoD was tested using a protocol based on CLSI EP17-A2.[21]

Limit of Quantitation

The Access AccuTnI+3 Limit of Quantitation (LoQ) is 0.04 ng/mL (µg/L) at 10%CV and 0.02 ng/mL (µg/L) at 20%CV. LoQ for Access AccuTnI+3 was determined using a protocol based on CLSI EP17-A2.[21] Multiple studies were completed, and a minimum of 60 replicates of several low concentration troponin I samples were measured in each study. The expected imprecision in the clinically relevant concentration range was estimated by combining data from multiple studies to create a best fit regression describing the relationship of %CV and troponin I concentration as shown in the table below.



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Access
Immunoassay Systems

BECKMAN COULTER

AccuTnI+3 CALIBRATORS

REF A98144 FOR USE ON ACCESS 2 IMMUNOASSAY SYSTEMS WITH TEST NAME: TnIA2

Intended Use

The Access AccuTnI+3 Calibrators are intended to calibrate the Access AccuTnI+3 assay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the Access 2 Immunoassay System to aid in the diagnosis of myocardial infarction.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert Relative Light Unit (RLU) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access AccuTnI+3 Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access AccuTnI+3 Calibrators (for use on Access 2 Immunoassay Systems)
Cat. No. A98144: S0–S1, 1.5 mL/vial; S2–S5, 1 mL/vial

- Provided ready to use.
- Freeze upon receipt at -20°C or colder.
- Mix contents **thoroughly** by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at -20°C or colder.
- After removing from -20°C storage, the thawed vials are stable at 2 to 10°C for 60 days. Label the vials with the date of thaw or the date of expiration.
- Return calibrators to 2 to 10°C after each use. Do not refreeze opened vials.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
S1, S2, S3, S4, S5:	Recombinant troponin complex at cTnI levels of approximately 0.3, 1.2, 5.0, 25 and 100 ng/mL (µg/L) in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
Calibration Card:	1

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Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[15]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

Run the Access AccuTnI+3 Calibrator S0 and S1 in quadruplicate, and the Calibrator S2–S5 in duplicate.

The Access AccuTnI+3 Calibrators are provided at six levels – zero and approximately 0.3, 1.2, 5.0, 25, and 100 ng/mL (μg/L). Assay calibration data are valid up to 56 days.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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