Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Summary Basis for Regulatory Action

Date: June 14, 2019

From: Susan A. Zullo, PhD, Chair of the Review Committee

BLA/ STN#: 125674.0

Applicant Name: Abbott Ireland Diagnostics Division

Date of Submission: March 29, 2018

Complete Response Letter: January 3, 2019

Resubmission: April 16, 2019

MDUFA Goal Date: June 16, 2019

Proprietary Name: Alinity s HBsAg and Alinity s HBsAg Confirmatory

Established Name (common or usual name): Antibody to Hepatitis B Surface Antigen (Mouse Monoclonal IgG and IgM) and Antibody to Hepatitis B Surface Antigen (Sheep)

Intended Use/Indications for Use: The Alinity s HBsAg assay is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum and plasma specimens on the Alinity s System. The Alinity s HBsAg assay is intended to screen individual human donors, including volunteer donors of whole blood and blood components, and other living donors for the presence of HBsAg. The assay is also intended for use in testing serum and plasma specimens to screen organ donors when specimens are obtained while the donor's heart is still beating, and in testing serum specimens to screen cadaveric (non-heart-beating) donors. It is not intended for use on cord blood specimens.

The Alinity s HBsAg Confirmatory assay is used to confirm the presence of hepatitis B surface antigen (HBsAg) in human serum and plasma by means of specific antibody neutralization on the Alinity s System. The assay is intended to be used for confirmation of samples found to be repeatedly reactive by the Alinity s HBsAg assay.

Recommended Action: The Review Committee recommends licensure of this product.

Review Office Signatory Authority: Nicole Verdun, M.D., Director, OBRR/CBER

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority: Mary A. Malarkey, Director, OCBQ/CBER

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Table 1 below indicates the material reviewed when developing the SBRA.

Table 1: Reviews Submitted

Document Title	Reviewer Name	Document Date
Product Review(s) (DETTD)		
• *Clinical*	Alain Debrabant	May 23, 2019
	Babita Mahajan	May 13, 2019
	Robert Duncan	May 7, 2019
• *Non-Clinical*	Krishnakumar Devadas	May 1, 2019
	Babita Mahajan	May 13, 2019
	Erica Silberstein	Apr 30, 2019
Statistical Review(s)		
• *Clinical*	Zhen Jiang	May 3, 2019
• *Non-Clinical*		
CMC Review		
• *CMC (DETTD)*	Krishnakumar Devadas	May 1, 2019
	Alain Debrabant	May 23, 2019
	Robert Duncan	May 23, 2019
	Erica Silberstein	Apr 30, 2019
• *Facilities Review (OCBQ/DMPQ)*	Nicole Li	Apr 29, 2019
• *Microbiology Review (OCBQ/DBSQC)*	Karla Garcia	Oct 25, 2018
• *Establishment Inspection Report(s) (OCBQ/DMPQ)*	Nicole Li	Dec 19, 2018
	Susan Zullo	Dec 19, 2018
Labeling Review(s)		
• *Product Office*	Susan Zullo	Jun 13, 2019
• *APLB (OCBQ/APLB)*	Dana Jones	May 14, 2018
Lot Release Protocols/Testing Plans	Marie Anderson	May 9, 2019
	Kori Francis	May 8, 2019
	Sean Younker	May 8, 2019

Bioresearch Monitoring Review	Colonious King	May 24, 2019
Software and Instrumentation Review	Lisa Simone Yongqing Chen	May 20, 2019 May 20, 2019
Tissues and Advanced Therapies (OTAT)	Brychan Clark	May 24, 2019

1. Introduction

The Alinity s HBsAg and Alinity s HBsAg Confirmatory assays are manufactured at the Abbott Ireland Diagnostics Division in Sligo, Ireland. This biologics license application (BLA) for Alinity s HBsAg and Alinity s HBsAg Confirmatory from Abbott Laboratories was received on March 30, 2018. The BLA was preceded by investigational new drug application (IND) 17632 received on July 28, 2017. An overview of the Alinity s System instrumentation and software is included in this original BLA submission.

Multiple pre-submission discussions on the regulatory pathway were conducted with FDA (May 18, 2012 - Type C Pre-IND meeting request; July 25, 2012- Face-to-Face Meeting with Abbott (CRMTS 8519); February 21, 2013 – Type B meeting (CRMTS 8793); July 30, 2015 – Pre-submission meeting telecon BQ150276; May 8, 2017 – Pre-submission meeting BQ170022). Multiple Pre-submission meetings (BQ170158; BQ180168) were conducted following the IND 17632 submission (July 27, 2017) to discuss issues related to the IND. The BLA was submitted on March 30, 2018.

Table 2: Chronological Summary of Submission and FDA Correspondence

Date	Action	Amendment to BL125674
Mar 30, 2018	BLA CBER receipt	
Apr 10, 2018	Acknowledgement Letter	
May 17, 2018	FDA IR from BIMO for data reformat	
May 22, 2018	Sponsor response to IR dated May 17, 2018	/0/2
May 23, 2018	Filing Notification Letter	
May 25, 2018	FDA IR on Software, DBSQC, and OTAT	
Jun 5, 2018	Telecon regarding risk documentation	
Jun 12, 2018	Sponsor response to IR dated May 25, 2018	/0/1
Jun 19 & 22, 2018	FDA IR - DBSQC; bioburden and lot release protocol	
Jun 27, 2018	Sponsor responses to IRs dated Jun 19 and Jun 22, 2018	/0/3
Jul 5, 2018	FDA advice email on risk management	
Jul 24, 2018	FDA IR on non-clinical studies	
Aug 7, 2018	FDA IR on design control	
Aug 8, 2018	Sponsor response to IR dated Jul 24, 2018	/0/4

Aug 15, 2018	Sponsor response to IR dated Aug 7, 2018	/0/5
Aug 16, 2018	Telecon regarding field actions and software updates	
Aug 23, 2018	FDA IR product and software	
Sep 12, 2018	Sponsor response to FDA IR dated Aug 23, 2018	/0/6
Sep 13, 2018	FDA IR on lot release protocol	
Sep 24, 2018	Sponsor response to FDA IR dated Sep 13, 2018	/0/7
Sep 24, 2018	FDA Form 483 Response	/0/8
Sep 25, 2018	Telecon regarding software versions and related IRs and proposal for precision, specificity, and sensitivity studies using software version 2.1.0	
Oct 4 & 9, 2018	FDA IRs from DMPQ – inspection-related	
Oct 9, 2018	Sponsor response to IR dated Aug 23, 2018	/0/9
Oct 18, 2018	Sponsor response to FDA IRs dated Oct 4 and Oct 9, 2018	/0/10 to /0/11
Oct 29, 2018	FDA IR (related to midcycle comments)	
Oct 30, 2018	FDA IR from DMPQ on software site installation	
Oct 30, 2018	Sponsor meeting materials/minutes from Jun 5, Aug 16, and Sep 25, 2018	/0/12
Nov 5, 2018	FDA IR from DMPQ – inspection-related	
Nov 6, 2018	Sponsor response to IR dated Oct 30, 2018	/0/13
Nov 8, 2018	FDA Response to Abbott telecon of Sep 25, 2018	
Nov 13, 2018	Sponsor response to IR dated Nov 5, 2018	/0/14
Nov 16, 2018	Sponsor Information on Studies with Software Update	/0/15
Nov 27, 2018	Sponsor materials for Nov 27, 2018 risk management telecon	/0/16
Dec 3, 2018	Sponsor response to IR dated Oct 29, 2018	/0/17
Dec 10, 2018	Advice Letter – Studies with software upgrade	
Dec 12, 2018	Sponsor response to FDA request on May 25, 2018, changes implemented from Jan 1, 2018 to Oct 20, 2018	/0/18
Jan 3, 2019	Complete Response Letter	
Jan 10, 2019	Telecon regarding lot release and email for clarification of CR Item 3	
Jan 15, 2019	Sponsor materials/meeting minutes from Jan 10, 2019 telecon on lot release	/0/19
Mar 11, 2019	Sponsor email about change to software version 2.5	/0/24

Apr 16, 2019	Sponsor response to CR	/0/20
April 25, 2019	Resubmission Classification Letter (Class 1)	
April 25, 2019	FDA email - updated Executive Summary	
May 3, 2019	FDA IR on software	
May 8, 2019	Sponsor response to IR dated May 3, 2019	/0/21
May 8, 2019	Sponsor response to IR dated May 3, 2019 (duplicate)	/0/22
May 8, 2019	Sponsor response to April 25, IR	/0/23
May 10, 2019	FDA IR for clarification of CR response Part II, Attachment 7.1	
May 15, 2019	Sponsor response to IR dated May 10, 2019	/0/25
May 17, 2019	FDA IR for CMC and labeling	
May 23, 2019	Sponsor response to IR dated May 17, 2019	/0/26
Jun 13 & 14, 2019	Final labeling	/0/27 to /0/28

2. Background

Hepatitis B virus (HBV) is the causative agent of hepatitis B that is transmitted through exposure to infected blood, semen, and other body fluids through parenteral, sexual, and perinatal routes. Transmission may also occur through transfusion of HBV-contaminated blood and blood products. After infection with HBV, HBsAg is the first antigenic marker that appears 1-12 weeks after exposure and 2-6 weeks before the onset of clinical symptoms. HBsAg persists during the acute phase and clears late in the convalescence period. HBsAg assays are used to screen blood and blood products to prevent transmission of HBV. These assays are also used to screen organ and tissue donors. The Alinity s HBsAg and Alinity s HBsAg Confirmatory assays are performed on a fully automated Alinity s System. The Alinity s HBsAg assay is for the qualitative detection of HBsAg in human serum and plasma using CMIA technology using the Alinity s System. Once the samples are loaded on the Alinity s System, all the reaction steps are performed by the system. Any sample that is identified as initially reactive is tested in duplicate by the system. Samples that are identified as repeatedly reactive are automatically tested by the Alinity s HBsAg Confirmatory assay.

3. Chemistry Manufacturing and Controls (CMC)

The manufacture of the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Alinity s HBsAg and Alinity s HBsAg Confirmatory assays are manufactured at the Abbott Ireland Diagnostics Division in Sligo, Ireland.

The Alinity s HBsAg Reagent Kit consists of the following components:

- Anti-HBs (mouse, monoclonal, IgM, IgG) coated microparticles

- Anti-HBs (mouse, monoclonal, IgG) and anti-HBs (goat IgG) acridinium-labeled conjugate
- Ancillary Wash Buffer

The Alinity s HBsAg Calibrator Kit consists of the following components:

- Calibrator 1 (inactivated, purified, human HBsAg, subtype *ad* in phosphate buffer with human plasma)
- Calibrator 2 (negative recalcified human plasma)

The Alinity s HBsAg Assay Control Kit consists of the following components:

- Negative Control (negative recalcified human plasma)
- Positive Control (inactivated, purified, human HBsAg, subtypes *ad* and *ay* in human plasma)

The Alinity s HBsAg Release Control Kit consists of the following component:

- Release Control (inactivated, purified, human HBsAg, subtypes *ad* and *ay* in human plasma)

The Alinity s HBsAg Confirmatory Reagent Kit consists of the following components:

- Pre-Treatment 1: Recalcified sheep plasma reactive for anti-HBs and recalcified human plasma
- Pre-Treatment 2: Recalcified human plasma and recalcified sheep plasma

The Alinity s System Bulk Solutions listed below are not part of any Alinity s assay kits, but are required to run the Alinity s assays on the Alinity s System

- Alinity Trigger Solution
- Alinity Pre-Trigger Solution
- Alinity s Concentrated Wash Buffer

Product Quality

b) Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the Alinity s HBsAg and Alinity s HBsAg Confirmatory kit were found to be adequate for their intended use.

c) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of Abbott Ireland Diagnostic Division's Alinity s HBsAg and HBsAg Confirmatory

assays is listed in the table below. The activities performed, and inspectional histories are noted in table 3 and are further described in the paragraphs that follow.

Table 3: Manufacturing Facilities Table for Alinity s HBsAg and HBsAg Confirmatory assays

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification /Results
Device Component Manufacturing, Finished Device Manufacturing, Instrument Solution Manufacture, Device Packaging/Labeling, QC and Release Testing Abbott Ireland Diagnostics Division Finisklin Business Park Sligo, Ireland F91VY44	3008344661	985724133	Pre-License Inspection	DMPQ August 21 – 27, 2018 VAI

CBER conducted a pre-license inspection (PLI) of Abbott Ireland Diagnostics Division from August 21 – 27, 2018. At the end of this inspection, a Form FDA 483 was issued. The firm has responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be resolved and the inspection was classified as voluntary action indicated (VAI).

e) Container Closure System

N/A

f) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Software and Instrumentation

The following is a summary overview of software, instrumentation and risk management information provided to support a reasonable assurance that the device is safe and effective for its intended uses and conditions of use.

Versioning: System Software v2.5.0. Assay Files HBsAg (List Number 06P02) version 150_002 and HBsAg Confirmatory (List Number 06P03) version 170_002.

Device Description: This fully-automated immunoassay analyzer is intended to perform high throughput routine and priority testing while allowing continuous access and automated retesting. The processing for each assay type is controlled by an assay-specific protocol, where parameter information is version-controlled. Positive sample ID is maintained with a barcode reader and all consumables are tracked for availability, stability and expiration. All consumables may be accessed for loading during normal assay operation, and liquid waste requires a laboratory drain outlet. The analyzer may interface with a Laboratory Information System to exchange test order information and results, and with a Laboratory Automation System to allow automated delivery of test samples, where sample ID is reconfirmed by barcode. The system is connected to the customer network with a required ethernet firewall for all external access. The Alinity PRO web-based application allows remote management of multiple instruments in one site. The AbbottLink application allows transfer of instrument data and system updates.

Risk Management: The final risk profile of the Alinity s System includes (b) (4) red (unacceptable) risks, (b) (4) yellow risks (that required assessment of acceptability) and (b) (4) green (acceptable) risks. Of the (b) (4) yellow risks, (b) (4) are related to false negative results (due to compromised consumables, incorrect instrument processing, and non-conforming lab facilities), and (b) (4) are related to a delay in donor results (due to user delay/interruption). The applicant stated that all risk control measures are implemented and verified and that the labeling notifies the user of residual risks. The applicant concluded the overall residual risk of the Alinity s System is Acceptable. This assessment appears to be supported by the evidence provided.

Short-term and long-term risks were evaluated related to donor test results, and to biological, chemical (including toxicological), physical and environmental hazards. Major hazards include: false positive and false negative screening results, delayed screening results, and various physical hazards to the operator (e.g., exposure to infectious materials; chemical, caustic or toxic exposure; slips, trips and falls; sharp/piercing object; clothing or jewelry entrapment; heat/hot parts/magnetic radiation; sprays and air borne matter; generation of metal azides that become explosive upon percussion; electricity; repetitive motion; manual handling of heavy items; and exposure to noise). Moderate hazards include inappropriate disposal of waste.

Significant risk controls for incorrect results include use of barcodes for sample and reagent tracking, sample and reagent handling quality checks, checks to detect errors in assay protocol execution, checks to minimize sampling errors (e.g., clot, fibrin and gel aspiration or short sampling). Labeling control measures to address use issues are also provided (e.g., instructions related to sample quality, sample preparation, material handling and storage). Control measures for delayed results focus on ensuring data are protected through power outages, minimizing use errors, and automated maintenance procedures. Cybersecurity risk control measures span those for confidentiality, integrity and availability; primarily user authentication, hardware firewall, operating system lockout (kiosk mode), encryption over the AbbottLink

connection, platform hardening and monitoring to isolate allowed functionality, and configuration management to ensure release of malware-free software.

Unresolved Anomalies: Software version v2.5.0 contains 210 non-safety-related open anomalies, and two safety-related open anomalies. The safety-related anomalies were both evaluated to represent low risk to the operator and no risk to the donor or recipient. In the first, the operator may be exposed to a chemical hazard, caused when a jam occurs in the loading of reaction vessels. The instrument provides an operator warning. There is no potential exposure to biohazard material, because no sample is present in the reaction vessel at that time. In the second case, the operator may be exposed to a chemical and/or biological hazard if a robotic collision inside the instrument occurs during a maintenance operation. When this situation was observed, the system detected the failure and issued a warning message. The manual contains operator information for chemical and biological hazards. Both defects will be corrected in the next software version.

Testing: Design verification was performed to confirm the design elements meet the specified requirements and includes verification of the effectiveness of risk control measures for potential causes of failure modes. This included software verification, software validation, and system integration. Over 600 protocols were performed. Representative test runs were provided, which corresponded to the highest risks identified in the system. System integration testing confirmed the Alinity s System met requirements using the Alinity s HBsAg and HBsAg Confirmatory assay reagents and assay files, and instrument accessories. A human-factors validation assessment identified two safety-related changes that required updates to the System Operations Manual (for proper handling of (b) (4)) and to the user interface (for search functionality of the On-line Help Browser). These changes were successfully validated. The assay files also met the acceptance criteria for unit (parameter) testing, integration testing, and system testing.

Development Management: The software development activities included establishing detailed software requirements, linking requirements with associate verification tests, verification and validation testing, defect tracking, configuration management and maintenance activities to ensure the software conforms to user needs and intended uses.

Review Issues and Device Changes for Safety and Effectiveness:

During this review, the following issues were raised and resolved to improve safety and effectiveness of the device:

1. System software was upgraded three times over the review cycle (for a total of six software versions) to address 12 CAPAs and 422 software changes. Eleven of these defects had the potential to impact assay results. Of the hardware changes made: six had the potential to impact EMC and/or safety certifications, and six had the potential to impact assay results. Adequate justification was provided to support the use of most previously-collected preclinical and clinical data to support this submission.

2. The applicant did not originally disclose the high risks associated with the system, which prevented a risk-based review.
    a. Risks processes were updated to comply with ISO 14971, and the improved risk documentation allowed the review to focus on the highest risks to use.
    b. As a result of the new risk process, the applicant stated several improvements are in progress; for example, to ensure risk control measures always have explicit requirements. This will ensure risk control measures are always implemented and verified.
3. Existing anomalies prior to v2.5.0 were reassessed based on the new risk management processes for their connection to risk controls and to system stability. A total of 167 software changes were made in the final version alone, where six had the potential to impact assay results.
4. The original submission was missing information related to the final assay file version, instrument and robot controls, discussion of how the device interoperates with other devices and software in the use environment, verification and validation for the highest risks in the system, impact of outstanding anomalies on system and assay performance, description of configuration management and maintenance to ensure malware free development and shipping, and documentation linking cybersecurity related risks to implemented controls. These were all provided, and all issues were resolved.

5. Analytical Studies

Non-clinical studies were performed at Abbott Diagnostics, Abbott Park, Illinois to evaluate the performance of the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays. The analytical studies were conducted in compliance with 21 CFR Part 58 (Good Laboratory Practices or GLPs), as applicable.

Sample Handling and Collection

a) Tube Type Equivalency and Matched Serum and Plasma

Assay performance when used to test blood specimens collected from individual donors in tubes containing: ACD-A, ACD-B, CP2D, CPDA-1, CPD, dipotassium EDTA, lithium heparin, sodium citrate, sodium heparin, dipotassium EDTA (plasma preparation tube), lithium heparin (plasma separator tube), serum (separator tube), and tripotassium EDTA was compared to performance when used to test specimens collected in serum tubes. Depending on the type of tube a minimum of (b) (4) nonreactive and (b) (4) HBsAg spiked reactive samples were tested in (b) (4) using the Alinity s HBsAg assay. A minimum of (b) (4) positive samples were tested (b) (4) using the Alinity s HBsAg Confirmatory assay. The data provided and reviewed demonstrate acceptable performance of the assays supporting the use of specimens collected in all tube types listed above.

HBsAg positive specimens from a minimum of (b) (4) individual donor sets were tested with a minimum of (b) (4) using the Alinity s HBsAg assay and tested (b) (4) using the Alinity s HBsAg Confirmatory assay. The data provided and reviewed demonstrate acceptable performance of the assays supporting the use of serum specimens or plasma specimens.

b) Specimen Storage

Assay performance when used to test serum and plasma specimens stored at various temperatures was evaluated. A minimum of (b) (4) nonreactive and (b) (4) HBsAg spiked reactive samples for each sample type were evaluated using the Alinity s HBsAg assay, with positive samples tested (b) (4) using the Alinity s HBsAg Confirmatory assay. For both reactive and nonreactive samples, the data provided and reviewed demonstrate acceptable performance of the assays supporting the use of serum and plasma specimens that have been stored at 30°C for up to 7 days, 2 to 8°C for up to 14 days, -20°C or colder for up to 3 months, and up to 6 freeze/thaw cycles.

c) Specimen Processing

Assay performance when used to test centrifuged non-frozen and previously frozen serum and plasma specimens was evaluated. A minimum of (b) (4) nonreactive and (b) (4) reactive samples for each sample type and each storage condition were evaluated. The data provided and reviewed demonstrate acceptable performance of the Alinity s HBsAg assay supporting the use of non-frozen and previously frozen serum and plasma specimens that have been tested up to (b) (4) hours after centrifugation at either 30,000 or 75,000 g-minutes.

Potentially Interfering Substances

a) Endogenous Interferences (Spiked)

Assay performance when used to test specimens containing high levels (spiked) of conjugated and unconjugated bilirubin, hemoglobin, triglycerides, or total protein was evaluated. A minimum of (b) (4) nonreactive and (b) (4) HBsAg spiked reactive samples for each interferent were evaluated with a minimum of (b) (4) using the Alinity s HBsAg assay. Positive samples were tested (b) (4) using the Alinity s HBsAg Confirmatory assay. The data provided and reviewed demonstrate acceptable performance of the assays for both nonreactive and reactive samples supporting the use of specimens containing up to 20 mg/dL of conjugated or unconjugated bilirubin, up to 500 mg/dL of hemoglobin, up to 3,000 mg/dL of triglycerides, and up to 12 g/dL of total protein. In addition, a negative and positive control were spiked with biotin to a concentration of 4,250 ng/mL. No interference was observed using the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays.

b) Endogenous Interferences (Native)

Assay performance when used to test specimens containing naturally occurring elevated levels of total bilirubin, hemoglobin, triglycerides or total protein were evaluated. (b) (4) to (b) (4) specimens for each interferent were used. Nonreactive and HBsAg spiked reactive samples with naturally occurring elevated levels of each interferent were compared to specimens with normal levels of each. The samples were tested using the Alinity s HBsAg assay and positive samples were tested (b) (4) using the Alinity s HBsAg Confirmatory assay. The data provided and reviewed demonstrate acceptable performance of the assays for both nonreactive and reactive samples supporting the use of specimens that contain greater than (b) (4) of total bilirubin (range tested (b) (4)), greater than (b) (4) of hemoglobin (range tested (b) (4)), greater than (b) (4) of triglycerides (range

tested (b) (4)), and greater than (b) (4) of total protein (range tested (b) (4)

Specific Performance Characteristics

a) Analytical Specificity (Other Disease States)

Assay performance when used to test specimens from individuals with other conditions or disease states (n = 191) unrelated to hepatitis B infection was evaluated (Table 4).

Table 4: Alinity s HBsAg and Alinity s HBsAg Confirmatory Other Disease States (Analytical Specificity) Summary

Other Disease States or Specimen Conditions	Alinity s HBsAg and HBsAg Confirmatory				(b) (4) HBsAg and HBsAg Confirmatory			
	Total	IR	RR	Confirmed RR	Total	IR	RR	Confirmed RR
Anti-HIV-1/HIV-2 Positive	10	1	1	1	10	1	1	1
Anti-HTLV I/II Positive	10	0	0	0	10	0	0	0
Anti-HCV Positive	10	0	0	0	10	0	0	0
Anti-HAV Positive	10	0	0	0	10	0	0	0
Co-infected CMV/EBV/HSV	10	0	0	0	10	0	0	0
Anti-HDV Positive	9	8	8	8	9	8	8	8
Anti-*T. pallidum* Positive	10	0	0	0	10	0	0	0
Non-viral Hepatitis	10	0	0	0	10	1	1	0
Rheumatoid Factor Positive	10	0	0	0	10	0	0	0
Anti-ds DNA Positive	10	0	0	0	10	0	0	0
Pregnant Females	14	0	0	0	14	0	0	0
Multiparous Females	10	0	0	0	10	1	0	0
Hyper IgG/IgM	10	0	0	0	7	0	0	0
Influenza Vaccine Recipient	10	0	0	0	10	0	0	0
Hemodialysis Patients	10	0	0	0	10	0	0	0
HAMA positive	10	0	0	0	10	0	0	0
Escherichia coli Infection	9	0	0	0	9	0	0	0
Heterophilic Antibody Positive	9	0	0	0	9	0	0	0
Fungal (Yeast) Infection	10	0	0	0	10	0	0	0
Total	**191**	**9**	**9**	**9**	**188**	**11**	**10**	**9**

Each specimen was tested (b) (4) using the Alinity s HBsAg assay and the (b) (4) HBsAg assay. The initial and repeat reactive rates were 4.71% (9/191). All nine of the repeatedly reactive specimens (one anti-HIV-1/HIV-2 and eight anti-hepatitis D virus (HDV)) were confirmed positive by both the Alinity s HBsAg Confirmatory and (b) (4) HBsAg Confirmatory assays. The anti-HDV results were expected since HDV requires HBV for replication. The study results for both the Alinity s HBsAg assay and (b) (4) HBsAg assay indicate a coinfection with HBV for the anti-HIV-1/HIV-2 repeatedly reactive specimen.

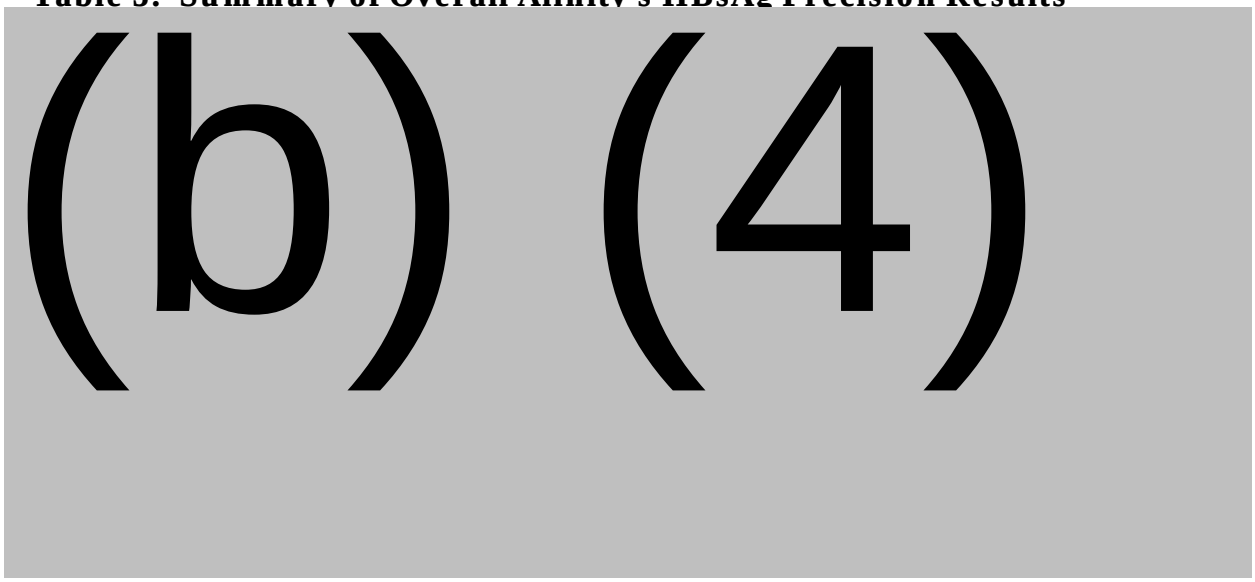
b) Precision

Alinity s HBsAg

Panels and controls were tested with a minimum of (b) (replicates (b) (times per day (separated by a minimum of (b) (4)) on (b) (instruments, on at least (b) (4) different days, for a minimum of (b) (4) required measurements. The within-laboratory imprecision results (which include within-run, between-run, and between-day variance

components), between-instrument imprecision results, and the reproducibility imprecision results (which include within-run, between-run, between-day, and between-instrument variance components) are presented in table 5. The Alinity s HBsAg assay using Alinity s System software version 2.5.0 demonstrated acceptable precision.

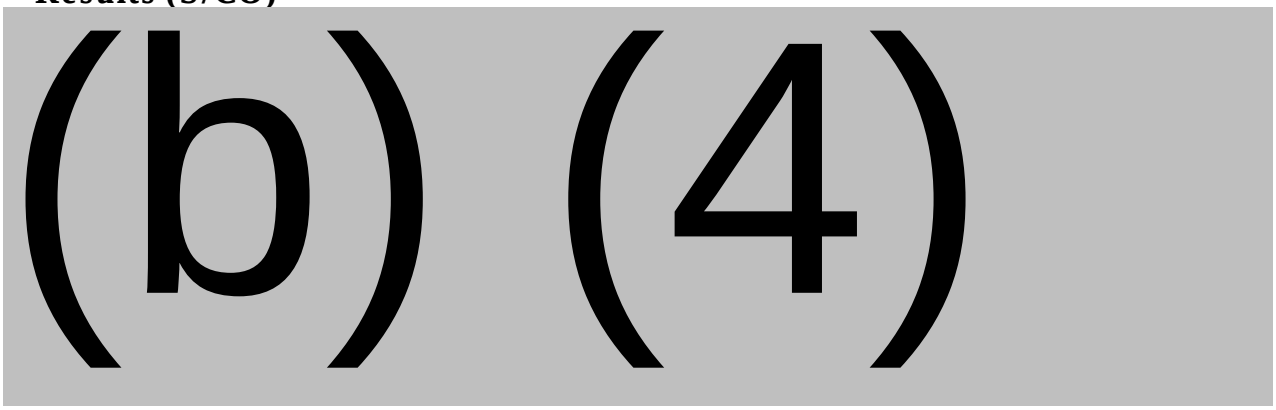
Table 5: Summary of Overall Alinity s HBsAg Precision Results



Alinity s HBsAg Confirmatory

Panels and controls were tested with a minimum of (b) (replicates (b) (times per day (separated by a minimum of (b) (4)) on (b) (instruments, on at least (b) (different days, for a minimum of (b) (4) required measurements. The within-laboratory imprecision results (which include within-run, between-run, and between-day variance components), between-instrument imprecision results, and the reproducibility imprecision results (which include within-run, between-run, between-day, and between-instrument variance components) are presented in tables 6 and 7. The Alinity s HBsAg Confirmatory assay using Alinity s System software version 2.5.0 demonstrated acceptable precision.

Table 6: Summary of Overall Alinity s HBsAg Confirmatory Precision Results (S/CO)



(b) (4)

Table 7: Summary of Overall Alinity s HBsAg Confirmatory Precision Results (% Neutralization)

(b) (4)

Review Issue: Abbott's original precision study using software version 1.2.0. was evaluated using (b) (4) instrument noting that: Each Alinity s System contains two process paths with two lanes per process path. All four lanes on one system were used in this study for both the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays. As each of the four lanes on one system has its own independent sets of wash zones and optics, the data for each lane were analyzed as a separate instrument. The review committee did not agree as many of the earlier steps in the assay such as reagent (b) (4) and sample (b) (4) are not separate for each process path. Further, the review committee conveyed to Abbott that Alinity s is a new instrument and the study fails to capture the precision among different instruments. A request to repeat the study was conveyed to the sponsor in an Information Request followed by a Complete Response letter dated January 3, 2019 because the study data had not yet been received. The precision study was repeated using (b) (4) separate Alinity s Systems with software version 2.5.0. The data from the new study were received in the response to the Complete Response letter on April 16, 2019 (Amendment 20) with acceptable variances among the instruments, and the issue was resolved.

c) In-House Specificity (Donors)

The specificity of the Alinity s HBsAg assay was determined by testing a minimum of (b) (4) plasma specimens from blood donors using three reagent kit lots. There were two initially reactive specimens and no repeatedly reactive specimens. The specificity of the Alinity s HBsAg assay was 100.00% (lower 95% confidence limit of 99.64%).

d) Genotype and Mutant Detection

The genotype detection of the Alinity s HBsAg assay and genotype confirmation using the Alinity s HBsAg Confirmatory assay were evaluated. Sixteen preselected HBsAg positive specimens of known genotypes A-H were tested (b) (4) using the Alinity s HBsAg assay and (b) (4) using the (b) (4) HBsAg assay. All 16

specimens were repeatedly reactive by both the Alinity s HBsAg and (b) (4) HBsAg assays and confirmed positive by both the Alinity s HBsAg and (b) (4) HBsAg Confirmatory assays. The mutant detection of the Alinity s HBsAg assay and genotype confirmation using the Alinity s HBsAg Confirmatory assay was also evaluated. Fifty-two preselected HBsAg positive mutant specimens (14 native and 38 recombinant) were diluted with recalcified negative human plasma to a target range of (b) (4) and tested (b) (4) using the Alinity s HBsAg assay. Each specimen was also tested (b) (4) on the (b) (4) HBsAg assay. All 52 specimens were repeatedly reactive and confirmed positive by the Alinity s HBsAg Confirmatory assay. The (b) (4) HBsAg assay only detected 38 of 52 specimens.

e) Analytical Sensitivity

The analytical sensitivity of the Alinity s HBsAg assay was evaluated using the WHO 3rd International Standard for HBsAg (subtypes *ayw1*/*adw2*, genotype B4, NIBSC Code 12/226). The standard was diluted to target concentrations between 0.005 and 0.100 IU/mL (0.03 ng/mL to 0.56 ng/mL) and tested with a minimum of (b) (4) replicates using three Alinity s HBsAg Reagent Kit lots. The analytical sensitivity was 0.013 IU/mL for all three reagent lots and ranged from 0.07 to 0.08 ng/mL.

f) Dilution Sensitivity

The dilution sensitivity of the Alinity s HBsAg assay and the (b) (4) HBsAg assay were compared. (b) (4) HBsAg reactive specimens were serially diluted with recalcified nonreactive human plasma to create samples with dilution factors ranging from (b) (4). (b) (4) neat and diluted samples were tested with a minimum of (b) (4) replicates using both the Alinity s HBsAg and (b) (4) HBsAg assays. The Alinity s HBsAg assay detected additional dilutions not detected by the (b) (4) HBsAg assay for (b) (4) of the (b) (4) positive specimens. For the remaining (b) (4) HBsAg positive specimens, the Alinity s HBsAg and (b) (4) HBsAg assays detected the same dilutions. Of the (b) (4) total dilutions, (b) (4) were reactive by the Alinity s HBsAg assay and (b) (4) were reactive by the (b) (4) HBsAg assay.

g) Limit of Detection

The limit of blank (LoB) and limit of detection (LoD) of the Alinity s HBsAg assay were evaluated. (b) (4)-analyte level samples were prepared by diluting the WHO 3rd International Standard for HBsAg to target concentrations between (b) (4) -analyte sample and (b) (4)-analyte level samples were tested in multiple replicates using (b) (4) Alinity s HBsAg assay lots on a minimum of (b) (4) days for a minimum of (b) (4) replicates of each sample. The maximum LoB value was (b) (4) and ranged from (b) (4). The maximum LoD value was (b) (4) and ranged from (b) (4).

h) Seroconversion

The seroconversion detection of the Alinity s HBsAg assay and Alinity s HBsAg Confirmatory assay were compared to the (b) (4) HBsAg assay. Twenty seroconversion panels were tested using the Alinity s HBsAg assay and the (b) (4) HBsAg assay. For one specimen, the first reactive timepoint was earlier for

the Alinity s HBsAg assay than for the (b) (4) HBsAg assay. This specimen was in the zone of equivalence for both assays (b) (4) It became reactive on (b) (4) HBsAg at the next timepoint. For each of the remaining 19 panel sets, the first reactive timepoint was the same for the Alinity s HBsAg assay and (b) (4) HBsAg assay. All Alinity s HBsAg repeatedly reactive specimens were confirmed positive by the Alinity s HBsAg Confirmatory assay.

i) Reagent Onboard Stability and Calibration Storage - Alinity s HBsAg and HBsAg C0nfirmatory

The performance of the Alinity s HBsAg and HBsAg Confirmatory assays when reagents are stored onboard the Alinity s System and the acceptability of a calibration generated using the Alinity s HBsAg assay and stored on the Alinity s System were evaluated. The reagents were subjected to transport/motion stress during shipping from the manufacturing site to the testing site. The Alinity s HBsAg Reagent Kit was used to generate Day 0 calibration, and both assays were stored onboard the Alinity s System. The HBsAg Panel prepared by diluting an HBsAg positive specimen to an S/CO target value of (b) (4), Negative Control, Positive Control, and Release Control tested at each timepoint were compared to the same samples at Day 0 with a minimum of (b) (4) replicates for (b) (4) timepoints for Alinity s HBsAg (b) (4) timepoints for Alinity s HBsAg Confirmatory) over a period of (b) (4) days (b) (4) days for Alinity s HBsAg Confirmatory). The data provided and reviewed demonstrate acceptable performance of the assays for all samples supporting the use of Alinity s HBsAg and HBsAg Confirmatory Reagent Kits that have been stored onboard the Alinity s System for (b) (4) days, and the use of a calibration generated using the Alinity s HBsAg assay and stored on the Alinity s System for up to 14 days.

j) Specimen Onboard Stability (Primary Tube)

The performance of the Alinity s HBsAg assay and the Alinity s HBsAg Confirmatory assay when used to test serum and plasma specimens stored onboard the Alinity s System in primary tubes was evaluated. A minimum of (b) (4) nonreactive and (b) (4) HBsAg spiked reactive samples for each sample type (serum and plasma (b) (4) were tested with a minimum of (b) (4) replicates using the Alinity s HBsAg assay and the positive samples tested (b) (4) using the Alinity s HBsAg Confirmatory assay. The nonreactive and reactive specimens stored for (b) (4) hours in primary tubes onboard the Alinity s System were compared to the same specimens tested at baseline. The data provided and reviewed demonstrate acceptable performance of the assays for both the nonreactive and reactive samples supporting the use of serum and plasma specimens that have been stored onboard the Alinity s System in primary tubes for up to 10 hours.

k) Specimen Onboard Stability (Sample Cup)

The performance of the Alinity s HBsAg assay and the Alinity s HBsAg Confirmatory assay when used to test serum and plasma specimens stored onboard the Alinity s System in sample cups was evaluated. The Alinity s HBsAg Negative Control and Positive Control were used for this study. Controls stored for > 3 hours in sample cups onboard the Alinity s System were compared to the same specimens tested at baseline. Each Control was pipetted into a minimum of (b) (4) sample cups for each

timepoint and tested (b) (4) using the Alinity s HBsAg assay. The Positive Control was tested (b) (4) using the Alinity s HBsAg Confirmatory assay. The data provided and reviewed demonstrate acceptable performance of the assays for both the Negative and Positive Controls supporting the use of serum and plasma specimens that have been stored onboard the Alinity s System in sample cups for up to 3 hours.

l) Reagent Cross Contamination

Potential cross contamination between assay reagents was evaluated by verifying the effectiveness of the Alinity s System reagent (b) (4) . A negative sample and HBsAg positive spiked sample were used for the study. The following assays were used as potentially contaminating assays to the Alinity s HBsAg: (b) (4) The following assays were used as potentially contaminating assays to the Alinity s HBsAg Confirmatory assay (Pre-Treatment 2): (b) (4) . The results demonstrated that the reagent (b) (4) are effective in controlling reagent cross contamination from a potentially contaminating Alinity s assay to the Alinity s HBsAg assay and the Alinity s HBsAg Confirmatory assay.

m) Within-Assay Carryover

The performance of the Alinity s HBsAg assay when exposed to potential within-assay sample carryover from a sample with high levels of HBsAg (b) (4) was evaluated by comparing the results of a protected negative sample to an unprotected negative sample. The protected negative sample was tested before a high positive sample, and the unprotected negative sample was tested after the high positive sample. (b) (4) Alinity s assays ((b) (4) were used in this study. The high positive sample was pipetted for each assay before the sample probe was cleaned to simulate a worst-case scenario for sample carryover. A total of (b) (4) iterations of alternating contaminating assay and susceptible assay were performed. The results demonstrated that no within-assay sample carryover was observed with the Alinity s HBsAg assay.

n) High Dose Hook Effect

The performance of the Alinity s HBsAg assay when used to test specimens containing high levels of HBsAg that have the potential to cause a hook effect was evaluated. A high positive sample with an HBsAg concentration of (b) (4) was (b) (4) with recalcified HBsAg and anti-HBs negative plasma to (b) (4) . The (b) (4) high positive sample and each (b) (4) were evaluated with a minimum of (b) (4) replicates. The data demonstrate the acceptable performance of the Alinity s HBsAg assay when used to test specimens containing high levels of HBsAg that have the potential to cause a high dose hook effect.

Stability

The stability studies were performed using a real-time stability study design. The studies were conducted through Month (b) (4) using (b) (lots each of Alinity s HBsAg Reagent Kit, Calibrator Kit, Assay Control Kit, Release Control Kit, and Alinity s

HBsAg Confirmatory Reagent Kit. The stability limits of the test were met for all lots for (b) (4) months allowing them to claim 12-month expiration dating. In addition, studies for the following stability conditions were also provided: (b) (4) lot of each assay component stored (b) (4) to cause (b) (4) between the product and the container closure), (b) (4) lot of calibrators, assay controls, and release control subjected to simulated customer-use conditions, with repeated cycles of opening, use, closure, and storage, including time the container is open when onboard the instrument), and (b) (4) lots of reagents and release control subjected to (b) (4) the instrument). Testing for these stability conditions has been completed through Month 12 and all criteria were met. The transport stability study was conducted through Month 12 using (b) lot each of the Alinity s HBsAg Reagent Kit, Calibrator Kit, Assay Control Kit, Release Control Kit, and Alinity s HBsAg Confirmatory Reagent Kit. All criteria were met.

Microbial Challenge

The following organisms were used in both the antimicrobial effectiveness and microbial interference studies. (b) (4)

a) Antimicrobial Effectiveness

The level of antimicrobial protection provided by the preservative system used in the components of the Alinity s HBsAg assay and the Alinity s HBsAg Confirmatory assay was evaluated. The assay kit components were (b) (4) listed above to a (b) (4) at each timepoint, evaluated, and compared to a control sample (b) (4) Bioburden levels were determined at (b) (4) days and (b) (4) days after (b) (4). The preservative was considered cidal if there was at least a (b) (4) log reduction in microbial counts between Day (b) (4) and Day (b) (4) and no increase greater than (b) (4) log between Day (b) (4) and Day (b) (4). The preservative was considered static if there was no increase greater than (b) (4) log in microbial counts between Day (b) (4) and Day (b) (4) or between Day (b) (4) and Day (b) (4) The results for all components were either cidal or static for all organisms.

b) Microbial Interference

The performance of the Alinity s HBsAg assay and Alinity s HBsAg Confirmatory assay was evaluated using kit components that had been exposed to (b) (4) All kit components were (b) (4) listed above to a (b) (4) and compared to control samples (b) (4) the components with (b) (4). All (b) (4) and control samples were stored for (b) (4) days at the recommended storage condition of (b) (4) and then tested within (b) (4) days after Day (b) (4). None of the components were sensitive to microbial contamination.

The combined results of the antimicrobial effectiveness and microbial interference studies show that all Alinity s HBsAg Reagent Kit, Calibrator Kit, Assay Control Kit,

Release Control Kit, and Alinity s HBsAg Confirmatory Reagent Kit components were adequately protected from microbial contamination through expiration for all organisms tested.

Cadaveric Studies

All cadaveric serum specimens used in the studies were previously frozen and stored frozen until their use. The living donor serum specimens used as control samples were either previously frozen or collected in-house and stored frozen after collection. Performance has not been established for the use of cadaveric blood specimens with the Alinity s HBsAg Confirmatory assay.

a) Cadaveric Reproducibility

The reproducibility of the Alinity s HBsAg assay when used to test cadaveric serum specimens was evaluated. A total of 24 cadaveric and 24 living donor serum specimens were tested (Table 8). The duration between the time of death and time of draw ranged from (b) (4) hour, (b) (4) minutes to 13 hours, (b) (4) minutes. Both random living donor and cadaveric serum samples were spiked with (b) (4) different HBsAg (b) (4) to create reactive samples. Samples were tested once daily for 6 days using 3 Alinity s HBsAg Reagent Kit lots for a total of 6 runs (n=18 total replicates per sample). The total %CV of 3.7 for the test cadaveric serum samples was less than the %CV of 5.3 for the living donor serum samples demonstrating acceptable reproducibility of the Alinity s HBsAg assay.

Table 8: Alinity s HBsAg Cadaveric Reproducibility

Specimen Category	Number of Replicates	Mean S/CO	Total [a] SD	CV
Cadaveric [b]	432	2.77	0.103	3.7
Living Donor	432	2.82	0.150	5.3

CV = coefficient of variation expressed as a percentage
SD = standard deviation
[a] Total variability contains within-specimen, between-lot, and lot-specimen interaction variance components.
[b] Cadaveric serum specimens were collected up to 13.7 hours after death.

b) Cadaveric Specificity

The specificity of the Alinity s HBsAg assay when used to test cadaveric serum specimens by comparing them to living donor specimens was evaluated. A total of 55 cadaveric and 55 living donor serum specimens were tested (Table 9). The duration between the time of death and time of draw ranged from (b) hour, (b) (4) minutes to 23 hours, (b) (4) minutes. Both random living donor serum samples and cadaveric serum samples were tested (b) (4) using three Alinity s HBsAg Reagent Kit lots. All samples were nonreactive. Specificity was 100.0% (55/55) for all reagent lots for both sample types with 95% confidence intervals of 93.51 to 100.00.

Table 9: Specificity in Cadaveric and Living Donors

Specimen Category	Lot	Nonreactive	Repeatedly Reactive	Specificity (%) (95% CI)
Cadaveric[a] (N=55)	Lot 1	55	0	100.00 (93.51 – 100.00)
	Lot 2	55	0	100.00 (93.51 – 100.00)
	Lot 3	55	0	100.00 (93.51 – 100.00)
Living Donor (N=55)	Lot 1	55	0	100.00 (93.51 – 100.00)
	Lot 2	55	0	100.00 (93.51 – 100.00)
	Lot 3	55	0	100.00 (93.51 – 100.00)

[a] Cadaveric serum specimens were collected up to 23.7 hours after death.

c) Cadaveric Sensitivity

The analytical sensitivity of the Alinity s HBsAg assay when used to test cadaveric serum specimens was evaluated. The duration between the time of death and time of draw ranged from (b) hour, (b) (4) minutes to 23 hours, (b) (4) minutes. Both random living donor and cadaveric serum samples were spiked with (b) (4) different HBsAg (b) (4) to create reactive samples. Samples were tested once within 24 hours of spiking using 3 Alinity s HBsAg Reagent Kits. All samples were reactive. Sensitivity was 100.0% for all reagent lots (Table 10) with 95% confidence intervals of 93.51 to 100.00 for cadaveric samples (55/55) and 93.40 to 100.00 for living donor samples (54/54).

Table 10: Analytical Sensitivity in Cadaveric and Living Donors by Lot

Specimen Category	Lot	Nonreactive	Mean S/CO	Sensitivity (%) (95% CI)
Cadaveric[a] (N=55)	Lot 1	55	2.92	100.00 (93.51 – 100.00)
	Lot 2	55	2.98	100.00 (93.51 – 100.00)
	Lot 3	55	3.02	100.00 (93.51 – 100.00)
Living Donor (N=54)	Lot 1	54	3.00	100.00 (93.40 – 100.00)
	Lot 2	54	2.99	100.00 (93.40 – 100.00)
	Lot 3	54	2.98	100.00 (93.40 – 100.00)

[a] Cadaveric serum specimens were collected up to 23.7 hours after death.

d) Cadaveric Specimen Storage

The performance of the Alinity s HBsAg assay when used to test cadaveric serum specimens that have been stored at various storage conditions was evaluated. The duration between the time of death and time of draw ranged from (b) (4) hours, (b) (4) minutes to 17 hours, (b) (4) minutes for the cadaveric serum samples used for the -20°C or colder storage condition and (b) hour, (b) (4) minutes to 22 hours, 54 minutes for the cadaveric serum samples used for other storage conditions. Random cadaveric serum specimens were spiked with (b) (4) different HBsAg (b) (4) (b) (4) to create reactive samples. Twelve nonreactive and 12 spiked reactive samples were used. Both sample types stored for a period of time at various storage temperatures were compared to samples tested at baseline. The samples were tested at least (b) (4) at each timepoint using the Alinity s HBsAg assay. For both nonreactive and reactive samples, the data provided and reviewed demonstrate acceptable performance of the assay supporting the use of cadaveric serum specimens that have been stored at approximately 30°C for up to 3 days, 2 to 8°C for up to 14 days, -20°C or colder for up to 3 months, and up to 6 freeze/thaw cycles.

6. Clinical

Clinical studies were conducted to evaluate assay specificity, sensitivity, and reproducibility to demonstrate performance and intended use of the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays. Testing was performed at four blood donor testing laboratories using specimens collected at three whole blood collection sites and one plasmapheresis collection site. A minimum of three lots each of the Alinity s HBsAg Reagent Kit, Alinity s HBsAg Calibrator Kit, Alinity s HBsAg Assay Control Kit, Alinity s Release Control Kit, and Alinity s HBsAg Confirmatory Reagent Kit were used for the studies at testing sites. The FDA-licensed (b) (4) HBsAg and (b) (4) HBsAg Confirmatory assays were used as the comparator tests.

Clinical Specificity

A prospective multicenter study was conducted to evaluate the clinical specificity of the Alinity s HBsAg assay on the Alinity s System using a total of 13,858 whole blood specimens from three sites. Of these, 7,347 were fresh serum and 6,511 were fresh plasma. An additional 3,135 plasmapheresis specimens were also collected from a separate site. The testing was performed using the Alinity s HBsAg assay and the (b) (4) HBsAg assay with their respective confirmatory assays, when necessary. There were no donor specimens that required a follow-up specimen to be collected. Specificity in blood and plasmapheresis donors was calculated to be 99.96% with a 95% confidence interval of 99.92% to 99.99% (Table 11). The final agreement between the Alinity s HBsAg and (b) (4) HBsAg assays was 99.96% (16,986/16,993).

Repeatedly reactive (RR) specimens were tested using the Alinity s HBsAg Confirmatory assay. Two specimens were confirmed positive. The six RR specimens

that were not confirmed by the Alinity s HBsAg Confirmatory assay were nonreactive by a commercially available HBsAg assay. The two confirmed positive specimens were positive by HBV Qualitative DNA. Those confirmed positive were excluded from specificity calculations.

Table 11: Alinity s HBsAg and Alinity s HBsAg Confirmatory Clinical Study Assay Reactivity

Category	Number Tested	IR (% of Total) (95% CI)	RR (% of Total) (95% CI)	Number Confirmed Positive (% of RR)	Specificity (%)[a] (95% CI)
Volunteer Blood Donors - Serum	7,347	7 (0.10) (0.04 - 0.20)	5 (0.07) (0.02 - 0.16)	2 (40.00)	99.96 (7,342 /7,345) (99.88 - 99.99)
Volunteer Blood Donors - Plasma	6,511	3 (0.05) (0.01 - 0.13)	3 (0.05) (0.01 - 0.13)	0 (0.00)	99.95 (6,508 /6,511) (99.87 - 99.99)
Total Volunteer Blood Donors	**13,858**	**10 (0.07) (0.03 - 0.13)**	**8 (0.06) (0.02 - 0.11)**	**2 (25.00)**	**99.96 (13,850 /13,856) (99.91 - 99.98)**
Plasmapheresis Donors	3,135	0 (0.00 - 0.12)	0 (0.00 - 0.12)	NA	100.00 (3,135 /3,135) (99.88 - 100.00)
Total Donors	**16,993**	**10 (0.06) (0.03 - 0.11)**	**8 (0.05) (0.02 - 0.09)**	**2 (25.00)**	**99.96 (16,985 /16,991) (99.92 - 99.99)**

IR = initially reactive; RR = repeatedly reactive; CI = confidence interval
[a] Specimens confirmed positive were excluded from specificity calculations

Clinical Sensitivity

Assay sensitivity was calculated by analyzing test results from frozen specimens provided by Abbott Laboratories. A total of 886 specimens was tested with the Alinity s HBsAg assay at three sites. These specimens were also tested at one site with the (b) (4) HBsAg assay. All RR specimens were tested with their respective confirmatory assay. The specimens used to assess assay sensitivity were: Preselected HBsAg Positive (previously confirmed positive using FDA-approved tests) – 167; Acute HBV Infection – 70; and Chronic HBV Infection – 195 for a total of 432 Preselected Positive specimens. The acute hepatitis B infection and chronic hepatitis B infection was based on four markers of hepatitis. In addition, 403 individuals from a population with increased risk for hepatitis B infection and 51 individuals who have recovered from HBV infection. Recovered HBV infection specimens were assumed HBsAg negative and were not included in the sensitivity analysis.

Sensitivity was estimated to be 100% for preselected positives (432/432) with a 95% confidence interval of 99.15% to 100.00%. All specimens confirmed positive by the Alinity s HBsAg Confirmatory assay.

There were three specimens from individuals at increased risk of HBV infection that were Alinity s HBsAg and (b) (4) HBsAg RR. All three confirmed positive by both confirmatory assays (Table 12).

Table 12: Alinity s HBsAg and Alinity s HBsAg Confirmatory Clinical Study Overall Sensitivity Summary

Specimen Category	N	Alinity s HBsAg		
		Number RR (% of Total)	Number Confirmed Positive (% of RR) (95% CI)	Sensitivity (%) (95% CI)
Preselected HBsAg Positive [a]	167	167 (100.00)	167 (100.00)	100.00 (167/167) (97.82, 100.00
Preselected HBsAg Positive - Acute HBV Infection [a]	70	70 (100.00)	70 (100.00)	100.00 (70/70) (94.87, 100.00)
Preselected HBsAg Positive - Chronic HBV Infection [a]	195	195 (100.00)	195 (100.00)	100.00% (195/195) (98.13, 100.00)
Subtotal	**432**	**432 (100.00)**	**432 (100.00)**	**100.00% (99.15, 100.00)**
Increased Risk of HBV Infection [b]	403	3 (0.74)	3 (100.00)	NA [d]
Recovered HBV Infection [c]	51	0 (0.00)	NA	NA
Total	**886**	**435 (49.10)**	**435 (100.00)**	**100.00% (435/435) (99.16, 100.00)**

N = number tested; NA = not applicable; RR = Repeatedly Reactive

[a] Preselected HBsAg positive specimens were previously confirmed positive by specific antibody neutralization using FDA-approved assays. Acute and chronic HBV classifications were determined using four HBV reference markers (HBsAg, anti-HBc IgM, total anti-HBc, and anti-HBs) or by medical diagnosis.

[b] The following risk factors were included: current or past residence in a hepatitis B endemic region, diagnosed or treated for a sexually transmitted disease, hemodialysis patient, heterosexual contact with a high-risk individual or an infected individual, history of incarceration, household contact with HBV infected individual, intravenous drug user, men who have sex with men, and multiple sex partners.

[c] Specimens were classified as recovered using four HBV reference markers (HBsAg, anti-HBc IgM, anti-HBc, and anti-HBs). Recovered HBV infection specimens were assumed HBsAg negative and were not included in the sensitivity analysis.

[d] The sensitivity calculation and confidence interval are not meaningful due to the small number of specimens.

Reproducibility Studies

The reproducibility of the Alinity s HBsAg assay and the Alinity s HBsAg Confirmatory assay was evaluated separately by testing the reproducibility panel

members shown in the tables below. Low and High HBsAg panel members were prepared by spiking human plasma with human-sourced material positive for HBsAg.

a) Alinity s HBsAg

Reproducibility of the Alinity s HBsAg assay was evaluated at three sites with (b) (4) instrument per site using three lots each of Alinity s HBsAg Reagent Kit, Alinity s HBsAg Calibrator Kit, Alinity s HBsAg Control Kit, and Alinity s Release Control Kit per CLSI EP15-A2. The Low HBsAg panel (Target S/CO (b) (4)), High HBsAg panel (Target S/CO (b) (4)), Negative Control (Target S/CO $\leq$ 0.70), and Positive Control (Target S/CO 1.42 to 7.25) were tested twice a day for 5 days in replicates of 4 at 3 sites using 3 lots each to obtain 360 replicates for each sample (i.e., 360 = 2 runs/day × 5 days × 4 replicates × 3 sites × 3 lots). The testing was conducted for 5 nonconsecutive days with a minimum of (b) (4) break of at least (b) day. Low and High HBsAg panel members were made by spiking recalcified human plasma with human-sourced material positive for HBsAg. There was 100% agreement observed in all four panel members (Table 13).

Table 13: Alinity s HBsAg Assay Agreement Results

Sample	N	≥ 1.00 S/CO	< 1.00 S/CO
		Agreement (%) (95% CI)	Agreement (%) (95% CI)
Low HBsAg	360	100.0 (360/360) (99.0 - 100.0)	NA
High HBsAg	360	100.0 (360/360) (99.0 - 100.0)	NA
Positive Control	360	100.0 (360/360) (99.0 - 100.0)	NA
Negative Control	360	NA	100.0 (360/360) (99.0 - 100.0)

The within-run, between-run, between-day, within-laboratory, between-site, and between-lot variance components were determined based on CLSI EP15-A2. For Low HBsAg, High HBsAg, and Positive Control, the overall %CV were 5.4%, 4.8%, and 4.6%, respectively. These are well below (b) (4) and are acceptable. These data demonstrate Alinity s HBsAg assay reproducibility across three sites with three lots of reagents across a range of reactivity (Table 14).

Table 14: Alinity s HBsAg Assay Variance Components Analysis Results

Sample	N	Mean S/CO	Within-Run		Between-Run		Between-Day		Within-Laboratory [a]		Between-Site		Between-Lot		Reproducibility [b]	
			SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Low HBsAg	360	1.70	0.080	4.7	0.000	0.0	0.010	0.6	0.081	4.8	0.000	0.0	0.032	1.9	0.091	5.4
High HBsAg	360	8.43	0.356	4.2	0.000	0.0	0.078	0.9	0.364	4.3	0.000	0.0	0.115	1.4	0.406	4.8

Positive Control	360	2.50	0.096	3.8	0.000	0.0	0.030	1.2	0.100	4.0	0.000	0.0	0.000	0.0	0.114	4.6
Negative Control	360	0.18	0.023	NA	0.019	NA	0.004	NA	0.030	NA	0.003	NA	0.000	NA	0.031	NA

N = number of replicates; NA = not applicable; CV = coefficient of variation expressed as a percentage; SD = standard deviation; %CVs are not meaningful when S/CO approaches zero

[a] Includes within-run, between-run, and between-day variability

[b] Includes within-in run, between-run, between-day, between-site, between-lot, and site-lot interaction variability

b) Alinity s HBsAg Confirmatory

Reproducibility of the Alinity s HBsAg Confirmatory assay was evaluated at three sites with (b) (4) instrument per site using three lots each of Alinity s HBsAg Reagent Kit, Alinity s HBsAg Confirmatory Kit, Alinity s HBsAg Calibrator Kit, Alinity s HBsAg Control Kit, and Alinity s Release Control Kit. Panel composition, testing strategy, and spiking are as described above.

The within-run, between-run, between-day, within-laboratory, between-site, between-lot, and site-lot interaction variance components were determined based on CLSI EP15-A2. For Low HBsAg, High HBsAg, and Positive Control, the overall %CV for S/CO are 5.6%, 4.8%, and 4.4%, respectively, and the overall %CVs for % neutralization are 6.6%, 1.1%, and 3.9%. These are well below (b) (4) and are acceptable. The mean percent neutralization was > 50% for the samples tested; and all Pre-Treatment 2 S/CO results were > 0.70 making all samples confirmed positive. These data demonstrate Alinity s HBsAg Confirmatory assay reproducibility across three sites with three lots of reagents across a range of reactivity (Table 15).

Table 15: Alinity s HBsAg Confirmatory Assay Variance Components Analysis Results for S/CO and % Neutralization

Sample	N	Mean S/CO [a]	Within-Run		Between-Run		Between-Day		Within-Laboratory [b]		Between-Site		Between-Lot		Reproducibility [c]	
			SD	CV	SD	CV	SD	CV	SD	CV	SD	%CV	SD	CV	SD	CV
Low HBsAg	360	1.75	0.081	4.6	0.015	0.9	0.028	1.6	0.087	4.9	0.000	0.0	0.038	2.2	0.098	5.6
High HBsAg	360	8.40	0.345	4.1	0.091	1.1	0.000	0.0	0.357	4.2	0.000	0.0	0.120	1.4	0.400	4.8
Positive Control	360	2.55	0.098	3.8	0.000	0.0	0.028	1.1	0.102	4.0	0.000	0.0	0.024	0.9	0.112	4.4

Sample	N	Mean %Neut	Within-Run		Between-Run		Between-Day		Within-Laboratory [b]		Between-Site		Between-Lot		Reproducibility [c]	
			SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Low HBsAg	360	94.98	3.913	4.1	0.705	0.7	0.673	0.7	4.032	4.2	1.421	1.5	3.822	4.0	6.275	6.6
High HBsAg	360	99.05	0.663	0.7	0.257	0.3	0.000	0.0	0.711	0.7	0.205	0.2	0.672	0.7	1.115	1.1
Positive Control	360	97.37	2.337	2.4	0.374	0.4	0.000	0.0	2.366	2.4	0.928	1.0	2.376	2.4	3.808	3.9

N = number of replicates; %Neut = % neutralization; CV = coefficient of variation expressed as a percentage; SD = standard deviation

[a] Pre-Treatment 2 S/CO

[b] Includes within-run, between-run, and between-day variability

[c] Includes within-run, between-run, between-day, between-site, between-lot, and site-lot interaction variability

Review Issues: The clinical studies submitted in the original BLA were completed using software version 1.2.0. Due to several changes in software versions that are described in the software and instrumentation section, smaller in-house studies to confirm the clinical sensitivity and specificity were requested to help determine if the upgrade to software version 2.5.0 had an effect on the previously evaluated performance of the assays.

In-House Specificity Study Comparing Software Versions

An in-house specificity study using 1,039 blood donor specimens obtained from specimen vendors (519 serum specimens and 520 plasma specimens, nonreactive for HBsAg and nonreactive by HBV (b) (4)) was performed on two Alinity s Systems with (b) (4) lot each of reagent kits, calibrators, and controls. The samples were tested on both the new (2.5.0) and the previous (1.2.0) software versions. The % agreement between the two software versions was 100.00% with a 95% confidence interval of 99.65% to 100.00%. One plasma specimen was repeatedly reactive, but not confirmed with both software versions. The remaining 1,038 specimens were nonreactive with both software versions. The Alinity s System software versions 1.2.0 and 2.5.0 demonstrated equivalent performance when used with the Alinity s HBsAg and HBsAg Confirmatory assays to test blood donor specimens.

In-House Sensitivity Study Comparing Software Versions

An in-house sensitivity study using positive specimens from the clinical studies (2-16-2441 and 2-16-2427) and seroconversion panel HBV11002, with the known positives being diluted to a range of (b) (4) was performed on software versions 1.2.0 and 2.5.0 to allow side-by-side comparison of results for each specimen. The study was performed using 27 sensitivity samples (2 positive samples from the clinical study, 6 panel members from a seroconversion panel, the 10-member CBER HBsAg Panel (b) (4) , and the 9-member CBER HBsAg Panel (b) (4) on two Alinity s Systems with (b) (4) lot each of reagent kits, calibrators, and controls. The samples were tested on both the new (2.5.0) and previous (1.2.0) software versions. For all samples, there was no qualitative difference in the final interpretation between software versions. All repeatedly reactive samples were confirmed positive with the Alinity s HBsAg Confirmatory assay with both software versions. The Alinity s System software versions 1.2.0 and 2.5.0 demonstrated equivalent performance when used with the Alinity s HBsAg and HBsAg Confirmatory assays to test sensitivity samples.

BIMO – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections of two clinical investigators did not reveal substantive problems that impact the data submitted in the application.

Pediatrics
N/A

Other Special Populations
N/A

7. Advisory Committee Meeting

N/A

8. Other Relevant Regulatory Issues

N/A

9. Labeling

The Advertising and Promotional Labeling Branch (APLB) found the proposed Instructions for Use (IFU), and the package and container labeling, acceptable from a promotional and comprehension perspective.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action
The Review Committee reviewed the original submission and related Amendments. A pre-licensure inspection was conducted and responses to the 483 observations were reviewed. All review issues have been resolved; therefore, the Review Committee recommends licensure of the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays.

b) Risk/Benefit Assessment
The benefit/risk analysis demonstrates that the benefit of the Alinity s HBsAg and Alinity s HBsAg Confirmatory assays outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 100% (95% CI of 95.151% - 100.00%), indicating a low probability of a false negative result. Among 16,993 blood and plasmapheresis donors tested with the Alinity s HBsAg assay, the assay specificity of 99.96% (95% CI of 99.92-99.99%) in clinical trials suggests a low probability of a false positive result. The Alinity s HBsAg and Alinity s HBsAg Confirmatory assays demonstrate comparable performance to the currently licensed (b) (4) HBsAg and HBsAg Confirmatory assays. However, the Alinity s HBsAg assay was able to detect more mutants compared to licensed (b) (4) HBsAg assay.

c) Recommendation for Postmarketing Activities
No postmarketing activities have been proposed for this application.