SUMMARY OF SAFETY AND EFFECTIVENESS

Product:

I. General Information

Device Generic Name: Human Immunodeficiency Virus (HIV) p24 antigen and antibodies to HIV Type 1 (HIV-1 group M and group O) and/or Type 2

Device Trade Name: ADVIA Centaur® HIV Ag/Ab Combo (CHIV) Assay

Product Code: MZF

Applicant's Name and Address: Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY, 10591-5097
Phone: 425 881-8300
Fax: 425 498-1651

Manufacturer: Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY, 10591-5097

Premarket Approval Application (PMA) Number: BP140103

Date of Panel Recommendation: Not Applicable

Office's Signatory Authority: Jay S. Epstein, 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.**

Date of Notice of Approval to the Applicant:

Material Reviewed/Consulted: The PMA, amendments to the PMA, and other specific documentation used in developing the Summary of Safety and Effectiveness (SSE)

Review memos from the following reviewers were used in developing the SSE:

Discipline reviewed	Reviewer names
Clinical and Non-clinical/Analytical	Andrew Dayton Luisa Gregori Subhash Dhawan Laure Juompan Diane Gubernot Babita Mahajan
Product Design	Krishnakumar Devadas
CMC (Chemistry, Manufacturing, and Controls)	Uros Djekic Bryan Grabias Xue Wang
Statistical	Chunrong Cheng
Facility and GMP	Jennifer Schmidt Deborah Trout
Bioresearch Monitoring	Christine Drabick
Labeling	Krishnakumar Devadas Dana Martin
Policy	Pradip Akolkar Indira Hewlett Sayah Nedjar J. Peyton Hobson

II. Intended Use

The ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay is an *in vitro* diagnostic immunoassay for the simultaneous qualitative detection of human immunodeficiency virus p24 antigen and antibodies to human immunodeficiency viruses type 1 (including group "O") and type 2, in serum using the ADVIA Centaur and ADVIA Centaur XP systems. The ADVIA Centaur CHIV assay is intended to be used as an aid in the diagnosis of HIV infection in pediatric and adult populations, including pregnant women.

The ADVIA Centaur CHIV assay is not intended for the screening of blood or plasma donors.

A reactive result using the ADVIA Centaur CHIV assay does not distinguish HIV-1 p24 antigen, HIV-1 antibody, HIV-2 antibody, and HIV-1 group O antibody.

CLIA Complexity: High

III. Description of the ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay

A. Device Description

The ADVIA Centaur CHIV assay is a two-wash antigen/antibody sandwich immunoassay in which antigens are bridged by antibody present in the patient sample and antigen (p24) in the sample is bridged by antibody present in the reagents. The ADVIA Centaur CHIV assay uses yeast derived recombinant antigens corresponding to the viral envelope proteins, synthetic peptides for the detection of antibodies to HIV-1 Group O and monoclonal antibodies specific to HIV-1 p24 antigen for the capture and detection of HIV-1 p24 antigen in the sample. The recombinant antigens used in this assay include an HIV-1 envelope protein (gp41/120) and an HIV-2 envelope protein (gp36).

The Solid Phase contains a preformed complex of streptavidin-coated paramagnetic microparticles and biotinylated HIV-1 and HIV-2 recombinant antigens, biotinylated group O peptide antigen, and biotinylated anti-p24 antibody. This reagent is used to capture anti-HIV-1 and/or HIV-2 antibodies and/or HIV p24 antigen in the patient sample. The Ancillary Lite Reagent and Lite Reagent contain acridinium ester labeled HIV-1 and HIV-2 recombinant antigens, acridinium ester labeled group O peptide antigen and acridinium ester labeled anti-p24 antibodies used to detect anti-HIV-1 and/or HIV-2 antibodies and/or p24 antigen bound to the Solid Phase in the sample.

A result of reactive or nonreactive is determined according to the Index Value established with the calibrators.

B. Components of ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay

a) Materials Provided

1. Reagent Pack
CHIV Primary Reagent Ready Pack contains the following reagents:

- *ADVIA Centaur CHIV Solid Phase (10.5 mL/reagent pack):* streptavidin-coated paramagnetic microparticles pre-formed with biotinylated HIV antigens (b)(4) µg/mL HIV-1 (b)(4), HIV-2 (b)(4), HIV-(b)(4) and antibody (b)(4) µg/mL anti-HIV-1 p24 antibody (b)(4) in buffer with bovine serum albumin, (b)(4) surfactant, and preservatives (b)(4)
- *Lite Reagent (5.5 mL/reagent pack):* recombinant HIV antigens (~0.1 µg/mL HIV-1 (b)(4), HIV-2 (b)(4) and HIV(b)(4) and antibodies (~0.004 µg/mL anti-HIV-1 p24 antibodies (b)(4) labeled with acridinium ester in buffer with bovine serum albumin, mouse IgG, goat serum, surfactant, and preservatives (b)(4).
- *Ancillary Lite Reagent (5.5 mL/reagent pack):* recombinant HIV antigens (b)(4) µg/mL HIV-1 (b)(4), HIV-2 (b)(4) and HIV(b)(4) and antibodies (~1.5 µg/mL anti-HIV-1 p24 antibodies (b)(4) labeled with acridinium ester in buffer with bovine serum albumin, mouse IgG, goat serum, surfactant, and preservatives (b)(4)
- *CHIV Low Calibrator (2.0 mL/vial):* defibrinated and filtered human plasma negative for antibodies to HIV and spiked with antibodies to HIV-1, heat inactivated goat serum, sodium azide (< 0.1%), and preservatives.
- *CHIV High Calibrator (2.0 mL/vial):* defibrinated and filtered human plasma negative for antibodies to HIV and spiked with antibodies to HIV-1, heat inactivated goat serum, sodium azide (< 0.1%), and preservatives.

2. ADVIA Centaur CHIV Master Curve card

3. ADVIA Centaur CHIV Calibrator Assigned Value cards

b) Materials required but not provided (available from Siemens as accessories to the Kit)

- *ADVIA Centaur Probe Wash 3 Sheath Fluid:* (b)(4) solution with the preservatives (b)(4)
- *ADVIA Centaur Wash 1 Wash Solution:* Sodium chloride, sodium phosphate, and (b)(4) solution with the preservatives (b)(4) and sodium azide (<0.1%).
- *CHIV Quality Control Sets**:*** ADVIA Centaur CHIV Quality Control Material is for in vitro diagnostic use to monitor the performance of the ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay on the ADVIA Centaur systems. The performance of the ADVIA Centaur CHIV quality control material has not been established with any other HIV assay.
    - *Negative Control:* Processed human plasma non-reactive to HIV with preservatives ProClin 300 (b)(4) sodium azide (<0.1%), (b)(4)

- *Positive Controls:* Processed human plasma, reactive for HIV-1, reactive for HIV-2, reactive for HIV-1 Group "O", and reactive for HIV-1 p24 antigen with preservatives ProClin 300 (b)(4) sodium azide (<0.1%), (b)(4)
- 1 vial of CHIV Positive anti-HIV-1 Control
- 1 vial of CHIV Positive anti-HIV-2 Control
- 1 vial of CHIV Positive anti-HIV-1 group O Control
- 1 vial of CHIV Positive HIV-1 p24 antigen Control

c) ***ADVIA Centaur Analyzer:*** The ADVIA Centaur CHIV assay is intended for use only with the ADVIA Centaur and ADVIA Centaur XP systems which are fully automated self-contained, immunoassay analyzers. The analyzer incorporates a dedicated software package for instrument control, data collection, results analysis, calibration and quality control. The ADVIA Centaur system has a throughput of up to 240 tests per hour and has a capacity to accommodate 180 samples and up to 30 reagent packs. The ADVIA Centaur XP system has a throughput of up to 240 tests per hour and can accommodate 1,000 samples and up to 30 reagent packs.

IV. Test Procedure

A. Specimen Collection, Preparation, and Storage

Collecting Specimens
The ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay can be performed on serum specimens collected using recommended procedures for collection of diagnostic blood specimens by venipuncture following the instructions provided with the specimen collection device for use and processing. Specimens are processed by centrifugation, typically followed by physical separation of the serum from the clot. The centrifugation step may occur up to 24 hours post draw. Complete clot formation should take place before centrifugation. Specimens with obvious microbial contamination should not be used.

Storing Specimens
The specimens should be tested as soon as possible after collecting. Processed specimens may be stored at 2° to 8°C if not tested within 24 hours of collection. Specimens that have been stored at room temperature for longer than 24 hours should not be used. Separated specimens are stable for 24 hours at room temperature, and up to 14 days at 2–8ºC. For longer storage, specimens may be frozen for up to 8 months at -20ºC or colder. Specimens may be subjected up to 5 freeze/thaw cycles. Specimens may be stored on the ADVIA Centaur and ADVIA Centaur XP systems for 8 hours. Serum samples in the primary tube (on-the-clot) without transferring to the secondary container can be stored in the primary tubes for up to 14 days.

B. Transporting Specimens

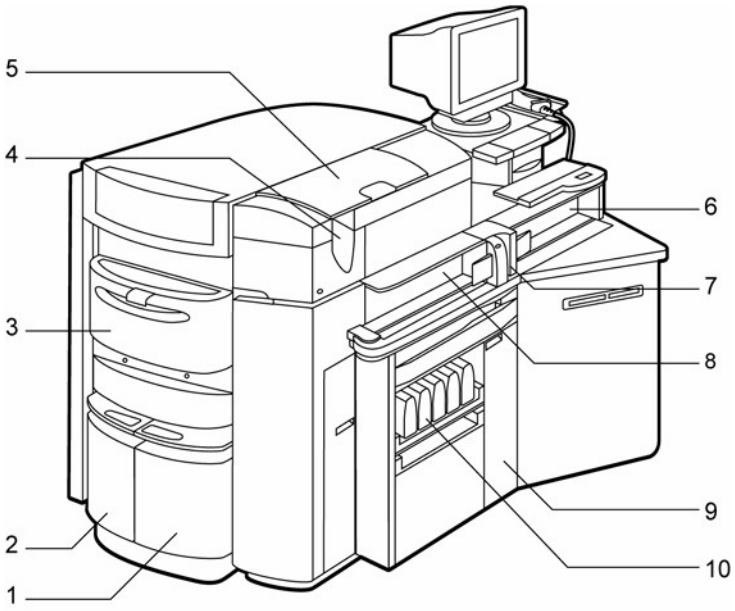
Processed specimens maintained at room temperature up to 24 hours or 2° to 8°C up to 14 days demonstrated no clinically significant differences. Specimens should be stored stoppered at 2° to 8°C upon arrival. Specimens should be shipped at 2–8°C or frozen.

C. Assay Procedure

The ADVIA Centaur and ADVIA Centaur XP systems automatically perform the following steps:

- Dispenses 100 µL of sample into a cuvette, and incubates for 6 minutes at 37°C.
- Dispenses 100 µL of Solid Phase and 50 µL of Ancillary Lite Reagent, and incubates for 18 minutes at 37°C.
- Separates the Solid Phase from the mixture, and aspirates the unbound reagent. Washes the cuvette with Wash 1.
- Dispenses 50 µL of Lite Reagent, and incubates for 18 minutes at 37°C.
- Separates the Solid Phase from the mixture, and aspirates the unbound reagent.
- Washes the cuvette with Wash 1.
- Dispenses 300 µL each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction.
- Reports results according to the selected option, as described in the system operating instructions.
- A result of reactive or nonreactive is determined according to the Index Value established with the calibrators.

ADVIA Centaur System



1	Water bottle	**6**	Sample exit queue
2	Waste bottle	**7**	Stat entry
3	Primary reagent compartment	**8**	Sample entry queue
4	Sample tip loader	**9**	Cleaning solution cabinet
5	Cuvette loader	**10**	System fluids

Figure1. The areas of the system that you can access while the system processes samples

D. Calibration

The ADVIA Centaur CHIV assay utilizes a two-point calibration (Low Calibrator, High Calibrator). The assay utilizes a factory-set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The Master Curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values on the system. The two calibrators in the kit are run when the lot is first used or after expiration of the calibration interval (21 days). Each calibrator is packaged with a lot-specific Calibrator Assigned Value card to facilitate entering the calibration values on the system. If the calibration run is valid as determined by prearranged parameters, the values are stored and used to "normalize" test values to the Master Curve. The Index value of the sample or control is read off the Master Curve. Samples that read at or above an Index of 1.0 are considered to be reactive for HIV.

E. Quality Control Procedure

The ADVIA Centaur CHIV controls are used for quality control of the ADVIA Centaur CHIV assay. The suggested expected values specific for the lot number of the controls are provided in the control package insert (Expected Value card). To monitor system performance and chart trends, as a minimum requirement, all ADVIA Centaur CHIV controls supplied in the CHIV control kit should be assayed at least once in every 24 hours that samples are analyzed. All control values should be within the index ranges specified in the control package insert. If any of the control results are outside of the specified index range, all test results generated since the last acceptable control results should be reevaluated for possible incorrect results. If any test results is adversely affected, the sample should be retested.

V. Interpretation of Test Results

Results of this assay should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

The system reports HIV antibody and/or p24 antigen results in Index Values and as reactive or nonreactive. The minimum level of antibodies to HIV-1/HIV-2 and/or p24 antigen that indicates reactivity is assigned an Index Value of 1.0. This is the Cut-off Index Value. The Cut-off Index Value of 1.0 is used to determine whether a specimen is reactive or nonreactive for p24 antigen and/or antibodies to HIV-1/HIV-2.

- Specimens with an Index Value of less than 1.0 are considered nonreactive for antibodies to HIV-1 and HIV-2 and p24 antigen by the ADVIA Centaur CHIV assay.

- Specimens with an Index Value greater than or equal to 1.0 are considered initially reactive for p24 antigen and/or antibodies to HIV-1 and/or HIV-2 and should be retested in duplicate after centrifugation at 10,000 x g for 10 minutes. If one or both of the duplicates are reactive, the specimen is repeatedly reactive by the ADVIA Centaur CHIV assay.
- Repeatedly reactive specimens must be investigated using supplemental tests for HIV-1 and/or HIV-2 and/or p24 antigen. In specimens giving indeterminate supplemental test results, testing of a subsequent sample drawn at a later date (such as 1–6 months) is recommended. For individuals who are indeterminate or confirmed positive for antibodies and/or p24 antigen, appropriate counseling and medical evaluation should be offered and is considered an important part of testing for antibody to HIV-1 and HIV-2 and/or p24 antigen.
- Specimens that are initially reactive are considered negative for HIV-1/HIV-2 antibodies and/or p24 antigen if both of the duplicates retest with an Index Value less than 1.0.
- The cut-off value for the ADVIA Centaur CHIV assay was verified based on results of Receiver-Operator characteristics (ROC) Curve.
- Interpretation of results was determined for this assay using the ADVIA Centaur system.

VI. Limitations of the Test

- The ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay is approved for In vitro diagnostic use only.
- This assay is not approved to screen blood or plasma donors.
- The ADVIA Centaur CHIV assay is limited to the detection of p24 antigen and/or antibodies to HIV-1 and/or HIV-2 in human serum.
- The calculated values for anti-HIV and/or p24 antigen in a given specimen as determined by assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay used. Values obtained with different assay methods cannot be used interchangeably. The reported antibody level and/or p24 antigen cannot be correlated to an endpoint titer.
- Heterophilic and Human Antibodies to Mouse antigens (HAMA) in human samples can react with reagent antibodies, interfering with in vitro immunoassays. Patients routinely exposed to animals or animal serum products for diagnosis or therapies can be prone to this interference and anomalous values may be observed. Specimens from patients who have received mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies and may interfere in assays that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.
- The performance of the ADVIA Centaur CHIV assay has not been established with cord blood, neonatal specimens, cadaver specimens, heat-inactivated specimens, or

body fluids other than serum such as plasma, saliva, urine, and amniotic or pleural fluids.

- The ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay may not detect all infected individuals. A negative test result does not exclude the possibility of exposure to or infection with HIV. HIV antibodies and/or p24 antigen may be undetectable in some stages of the infection and in some clinical conditions.
- A person who has antigen or antibodies to HIV is presumed to be infected with the virus. However, a person who has participated in an HIV vaccine study may develop antibodies to the vaccine and may or may not be infected with HIV.

VII. Marketing History

The ADVIA Centaur CHIV Assay is currently being marketed internationally in accordance with section 802 of the FD&C Act. This product has not been withdrawn from any country for any reason.

VIII. Potential Adverse Effects of the Device on Health

Potential adverse effects of the ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay relate to the risk of false positive and false negative results. While performance studies indicate that this risk is likely to be very small, the potential for inaccurate results exists. The risk of incorrect results is minimized by following the procedures and instructions outlined in the Package Insert.

IX. Summary of Preclinical Studies:

HIV-1 p24 Antigen Analytical Sensitivity

Analytical sensitivity of the ADVIA Centaur CHIV assay to HIV-1 p24 antigen was determined using 1st International Reference Reagent, NIBSC code 90/636 and a Zeptometrix standard in HIV negative human serum.

Results: The antigen sensitivity was tested using a standard from the Zeptometrix EIA kit with 5 lots of reagents and demonstrated a mean sensitivity of 9.04 pg/mL to HIV-1 p24 Antigen (range 6.1 to 11.4 pg/mL). The analytical sensitivity was also verified with the HIV-1 p24 1st International Reference Reagent, NIBSC code 90/636 and demonstrated a mean sensitivity of 1.05 IU/mL to the HIV-1 p24 Antigen (values that ranged from 0.74-1.39 IU/mL).

Detection HIV-1 and HIV-2 Antigens in (b)(4)

Forty seven HIV-1 viral isolates and one HIV-2 viral lysate were tested using the ADVIA Centaur CHIV assay, and were reactive.

Results: Of the 47 HIV-1 and one HIV-2 (b)(4) samples tested, 100% (48/48) were reactive. The results demonstrate acceptable performance.

Table 1: Detection HIV-1 and HIV-2 Antigens in (b)(4)

Viral Lysate Subtype	Number Tested	Number Reactive
HIV-1 A	2	2

Viral Lysate Subtype	Number Tested	Number Reactive
HIV-1 B	10	10
HIV-1 C	7	7
HIV-1 D	3	3
HIV-1 F	4	4
HIV-1 G	2	2
HIV-1 AE	10	10
HIV-1 AG	3	3
HIV-1 O	2	2
HIV-1 IIIB	2	2
HIV-1 strain Mn & BA-L	2	2
HIV-2 NIHZ	1	1
Total	48	48

Table 1 summary: All 47 HIV-1 and one (1) HIV-2 (b)(4) samples tested were reactive.

Seroconversion Panels
The ADVIA Centaur CHIV assay was evaluated with fifteen (15) commercially available seroconversion panels that were evenly divided among three testing sites. The panels were tested with the ADVIA Centaur CHIV assay and an FDA approved HIV assay.

Results: ADVIA Centaur CHIV assay detected more reactive bleeds (n=38) than the FDA approved HIV Ab assay. The results demonstrate acceptable performance.

Table 2: ADVIA Centaur CHIV Assay Reactivity in HIV-1 Seroconversion Panels

Number of Reactive Panel Members				Days to First Reactive Result		
Panel ID	**Number Tested**	**ADVIA Centaur CHIV Assay**	**FDA Approved HIV Ab Assay**	**ADVIA Centaur CHIV Assay**	**FDA Approved HIV Ab assay**	**Difference in Days to First Reactive Result (Based on Bleed Date)[a]**
PRB926	6	4	2	7	27	20
PRB940	8	7	7	7	7	0
PRB942	4	1	0	14	--[b]	--[b]
PRB943	7	4	2	12	19	7
PRB946	4	2	0	7	--[b]	--[b]
PRB948	4	1	0	23	--[b]	--[b]
PRB954	7	2	1	17	21	4

Number of Reactive Panel Members				Days to First Reactive Result		
Panel ID	**Number Tested**	**ADVIA Centaur CHIV Assay**	**FDA Approved HIV Ab Assay**	**ADVIA Centaur CHIV Assay**	**FDA Approved HIV Ab assay**	**Difference in Days to First Reactive Result (Based on Bleed Date)[a]**
PRB955	5	3	1	7	14	7
PRB956	5	2	1	47	50	3
PRB960	9	2	0	28	--[b]	--[b]
PRB961	9	2	0	27	--[b]	--[b]
PRB962	6	2	0	14	--[b]	--[b]
PRB963	7	2	0	17	--[b]	--[b]
PRB964	6	1	0	22	--[b]	--[b]
PRB966	10	3	2	44	48	4
Total	97	38	16	NA[c]	NA	NA

[a] The dates of the first reactive test results were compared for the FDA approved HIV Ab assay and the ADVIA Centaur CHIV assay. If the first reactive test result occurred on the same day, then the difference is 0; if ADVIA Centaur CHIV assay had an earlier date, then the difference is positive; if ADVIA Centaur CHIV assay had a later date, then the difference is negative.
[b] All bleeds in these panels were nonreactive with the FDA approved HIV Ab assay.
[c] NA = Not applicable

Table 2 summary: ADVIA Centaur CHIV assay detected 22 more reactive bleeds compared to the FDA approved HIV Ab assay.

HIV-1 Subtype Panel

In a study of HIV-1 Group M subtypes and HIV-1 group O, 45 worldwide antibody specimens were tested with the ADVIA Centaur CHIV assay.

Results: This subtype antibody panel was reactive in 100% (45/45) of the members on the ADVIA Centaur CHIV assay and FDA approved HIV Ab assay. The results demonstrate acceptable performance. The results are shown in table 3.

Table 3: ADVIA Centaur CHIV Assay Reactivity with HIV-1 Subtypes

HIV-1 Subtype	Number Tested	Number Reactive
A	2	2
B	3	3
C	2	2
D	3	3
E	4	4
F	4	4
G	4	4
H	1	1

HIV-1 Subtype	Number Tested	Number Reactive
J	1	1
A1	2	2
F2	2	2
O	5	5
CRF01-AE	4	4
CRF02-AG	4	4
CRF06	2	2
CRF11	1	1
CRF13	1	1
Total	45	45

Table 3 summary: All 45 panel members tested reactive

Dilutional Sensitivity

Dilutional Sensitivity of the ADVIA Centaur CHIV assay was evaluated using (b)(4) sets of HIV-1 and (b)(4) sets of HIV-2 serial dilutions. Each set was prepared using (b)(4) samples with high HIV-1 or HIV-2 antibody index (with approximate concentration between (b)(4) and serially diluting it with a negative sample with index values (b)(4), of the assay range). Each dilution series contained a total of (b)(4) dilutions. Dilution samples were run in duplicate on one ADVIA Centaur using one lot of ADVIA Centaur CHIV reagent and the observed results were compared with the results obtained using a commercially available FDA approved HIV Ab assay.

Results: For all but one HIV-1 sample, the results were reactive on the CHIV assay at the same or greater dilution as the FDA approved HIV Ab assay. For one sample, 1746217, the CHIV assay was reactive at a 1/16 dilution compared to the FDA approved HIV Ab assay which was reactive at a dilution of 1/32. For all HIV-2 samples, the results were reactive on the CHIV assay at the same or greater dilution as the FDA approved HIV Ab assay. The results demonstrate acceptable performance.

Hook Effect

The ADVIA Centaur HIV Ag/Ab Combo (CHIV) Immunoassay was evaluated for "high Index hook" effect in specimens containing extremely high HIV titers. (b)(4) HIV-1 high titer positive serum specimens and (b)(4) high titer HIV-2 positive specimens in EDTA plasma and purified recombinant p24 antigen up to a concentration of 1 mg/mL were evaluated.

Results: Results obtained indicated that the ADVIA Centaur CHIV assay did not exhibit a high-dose hook effect up to the levels tested. The results demonstrate acceptable performance.

Effect of Potentially Interfering Substances

The ADVIA Centaur CHIV assay was tested for interference due to high levels of endogenous substances. For each endogenous substance level; a negative sample (neat), an HIV-1 antibody sample, an HIV-2 antibody sample, an HIV-1 Type O antibody sample and an HIV antigen sample was assayed. All positive samples tested were generated by spiking the analyte into a

confirmed negative (neat) donor sample to a target Index ranging between 2 and 4. These specimens were spiked with the interferents and assayed.

Table 4: ADVIA Centaur CHIV Assay Reactivity with Potentially Interfering Substances

Serum Specimens That Are	Demonstrate ≤ 10% Change in Results Up To
hemolyzed	500 mg/dL of hemoglobin
lipemic	1000 mg/dL of triglycerides
icteric	40 mg/dL of conjugated bilirubin
icteric	40 mg/dL of unconjugated bilirubin
proteinemic	3.5 g/dL of protein[a]
hyper-IgG	60 mg/mL of immunoglobulin G
hyperproteinemic	12 g/dL of protein
cholesterol	400 mg/dL
biotin	500 ng/mL

[a] Demonstrates ≤ 10% change in results with protein as low as 3.5 g/dL.

Table 4 summary: The performance of the assay was not affected by cross reacting substances that may be present in clinical samples.

Results: None of the interferents at the levels tested produced a change in the interpretation of the assay. The results demonstrate acceptable performance.

Table 5: ADVIA Centaur CHIV Assay Cross reactivity with Unrelated Medical Conditions

Clinical Category	Number of Reactive Results		
	Number Tested	ADVIA Centaur CHIV	FDA Approved HIV Ab Assay
Alcoholic Hepatitis	5	1	1[a]
Anti-Nuclear Antibody (ANA)	9	0	0
Crohn's Disease	10	0	0
Cytomegalovirus IgG	5	0	0
Cytomegalovirus IgM	10	0	0
Diabetes	10	0	0
E.coli Ag	1	0	0
Epstein-Bar virus (EBV) IgG	5	0	0
Epstein-Bar virus (EBV) IgM	10	0	0
Fibromyalgia condition	10	0	0
Flu Vaccine Recipient	22	0	0
Graves' Disease	8	0	0
Human anti-mouse antibodies (HAMA)	18	0	0

Clinical Category	Number of Reactive Results		
	Number Tested	ADVIA Centaur CHIV	FDA Approved HIV Ab Assay
Hepatitis C virus (HCV) Ag	5	0	0
Hepatitis A virus (HAV) IgM	5	0	0
Hepatitis B Surface Ag (HBsAg)	10	0	0
Hepatitis C virus (HCV) Ab	10	0	0
Herpes Simplex virus (HSV1/2) IgG	5	0	0
Herpes Simplex virus (HSV1/2) IgM	10	0	0
High Human Immunoblobin IgA	11	0	0
High Human Immunoblobin IgG	13	0	0
High Human Immunoblobin IgM	9	0	0
Human T-cell Lymphotropic virus (HTLV I)	10	0	0
Mixed Connective Tissue Disease (MCTD)	9	0	0
Rheumatoid Factor positive	10	0	0
Rubella IgG	10	0	0
Rubella IgM	10	0	0
Scleroderma	10	0	0
Staphylococcus Aureus Ag	1	0	0
Syphilis IgG	9	0	0
Syphilis IgM	10	0	0
Systemic Lupus Erythematosus (SLE)	9	0	0
Toxo IgG	10	0	0
Toxo IgM	12	0	0
Ulcerative colitis	9	0	0
Varicella Zoster Virus (VZV) IgG	10	0	0
MPO and PR3 for Vasculitis	10	0	0
Candidiasis (yeast infection)	5	0	0

[a] The reactive alcoholic hepatitis sample was confirmed as HIV-1 positive by testing with an FDA approved differentiation assay.

Table 5 summary: CHIV assay had 100% agreement with the FDA approved HIV Ab assay.

Effect of Unrelated Medical Conditions

Three hundred and forty-five (345) samples from thirty-eight (38) groups of potential cross-reactants were evaluated for potential cross reactivity with the ADVIA Centaur CHIV assay. The reactive HIV status of each specimen was verified using a commercially available FDA approved HIV Ab assay.

Results: Of the total 345 samples, one alcoholic hepatitis sample was reactive on both the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay. The remaining 344 samples were non-reactive on both the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay. The CHIV assay had 100% agreement with the FDA approved HIV Ab comparison assay.

The performance of the assay was not affected by cross reacting substances that may be present in clinical samples or by interfering substances. The results demonstrate acceptable performance.

Instrument Studies

i. Environmental Testing

Environmental testing was performed to assess ADVIA Centaur CHIV assay control recovery at the mean and extreme environmental conditions as specified in the ADVIA Centaur User's Guide. Each assay is calibrated and run on a single ADVIA Centaur in an environmental chamber set at 18°C, 24°C and 30°C. The percent change in control recovery per degree is calculated. The studies demonstrated acceptable performance of the ADVIA Centaur CHIV assay when performed on instruments operating at the extremes of the temperature range for the ADVIA Centaur system (18°C to 30°C).

ii. Reagent Compatibility Testing

The ADVIA Centaur CHIV assay was evaluated for its potential effect on all other assays using the same reagent probe and for the effect of all the other assay reagents using the same reagent probe on the ADVIA Centaur CHIV assay. Mitigations have been successfully developed for all interferences observed and have been implemented through revisions to the ADVIA Centaur CHIV Test Definition. Mitigation of any interference identified is accomplished through Test definition (TDef) scheduling options, using multiple water washes, or a Wash Pack with a solution other than water.

Reproducibility

The reproducibility of the ADVIA Centaur Combo HIV assay was evaluated utilizing a total of three reagents lots. Each site utilized two reagent lots. An 8-member panel was assayed in replicates of 4 with 2 runs per day over 5 days for each lot (n = 240 for each sample). The panel members consisted of HIV-1 antibody low and high positive samples, HIV-2 antibody low and high positive samples, p24 antigen low and high positive samples, one HIV-1 Group O antibody positive sample and one HIV negative sample. Calibrators (tested as unknown samples) and controls were run in parallel in replicates of 4. The results are shown in table 6.

Results: Precision and reproducibility of the ADVIA Centaur CHIV assay was acceptable demonstrating only minor variability from run to run, day to day or reagent lot to reagent lot. The total CV for the panel members ranged below the acceptance specification of (b)(4) for the ADVIA Centaur CHIV assay.

Table 6: Summary of Precision and Reproducibility of the ADVIA Centaur CHIV Assay

	Mean	Within run Repeatability		Between run		Between Day		Within Site and Lot		Between Site		Between Lot		Total Precision (Within Lab)	
Specimen type	Index	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Negative Pool	0.77	0.02	NA	0.04	NA	0.01	NA	0.05	NA	0.02	NA	0.06	NA	0.08	NA
Low HIV-1 Pool	1.27	0.03	2.7	0.06	4.7	0.00	0.0	0.07	5.5	0.03	2.5	0.07	5.8	0.11	8.3
High HIV-1 Pool	3.80	0.08	2.1	0.20	5.3	0.09	2.5	0.24	6.2	0.10	2.5	0.11	2.9	0.28	7.3
Low HIV-2 pool	1.34	0.04	3.2	0.06	4.4	0.00	0.0	0.07	5.4	0.06	4.4	0.08	5.8	0.12	9.0
High HIV-2 Pool	3.60	0.11	3.0	0.14	4.0	0.00	0.0	0.18	5.0	0.11	3.0	0.17	4.8	0.27	7.5
Type O Pool	3.07	0.13	4.4	0.16	5.1	0.00	0.0	0.21	6.7	0.13	4.2	0.25	8.2	0.35	11.4
Low p24 Pool	2.91	0.08	2.8	0.14	4.9	0.02	0.6	0.16	5.7	0.11	3.8	0.39	13.3	0.43	14.9
High p24 Pool	5.64	0.16	2.8	0.26	4.6	0.11	2.0	0.33	5.8	0.15	2.6	1.04	18.4	1.10	19.4

Table 6 summary: Precision and reproducibility of the ADVIA Centaur CHIV assay was acceptable demonstrating only minor variability from run to run, day to day or reagent lot to reagent lot.

Reagent, Calibrator, and Control Stability

- A real-time stability study was carried out according to the protocol specifications for the ADVIA Centaur ReadyPack reagents, calibrators, and controls. Data were provided for up to (b)(4) months for four lots to support a 10 month shelf life when stored at 2-8°C.
- Onboard stability testing was conducted with four lots of the ADVIA Centaur CHIV reagents. The data obtained support onboard storage for 42 days and a 21 day recalibration for the ADVIA Centaur CHIV reagents.

- Open vial (in-use) stability studies for the calibrators and controls were performed with three lots of calibrators and controls. The data provided indicates that the calibrators and controls are stable for (b)(4) days after the vials are first opened.
- Shipping studies for the ADVIA Centaur CHIV assay reagents indicated that the product tolerated (b)(4) Additionally, the reagents were subjected to temperature stress (b)(4) . Based on these studies, the recommended shipping conditions are to ship the ADVIA Centaur CHIV reagents stored at (b)(4)
- Calibrators and controls were subjected to temperature stress (b)(4) . Based on these studies, the recommended shipping conditions are to ship the ADVIA Centaur CHIV calibrators and controls at (b)(4)

X. Summary of Clinical Studies:

Specificity

Samples from Low Risk Individuals

A multisite clinical study was performed to compare the specificity of the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay. HIV confirmatory testing was performed using FDA approved HIV-1 Western Blot, HIV-2 EIA and HIV-1 RNA PCR tests and using research use-only HIV-2 Western Blot and HIV-1 p24 Antigen assays. The specificity of the ADVIA Centaur CHIV Assay was determined in patients who were at low risk for HIV infection. The low-risk population (6140 specimens) included 5746 specimens from apparently healthy subjects and 254 specimens from pregnant females. Of the 254 specimens from pregnant females, 157 were prospectively collected and 97 were retrospectively collected. The remaining 140 specimens in the low risk population included 110 low risk pediatric subjects and 30 hospitalized patients, all of which were prospectively collected. Of the 19 CHIV repeatedly reactive specimens, 7 specimens were also reactive with the FDA approved HIV Ab assay. Two (2) specimens repeatedly reactive with the CHIV and FDA approved HIV Ab assay from the apparently healthy population were confirmed positive for HIV-1 by Western Blot. The results from these 2 specimens were excluded from the specificity calculation.

Table 7: Reactivity in Low Risk Individuals

	ADVIA Centaur CHIV Assay				**FDA Approved HIV Ab Assay**			**Repeatedly Reactive Specimens (Number Reactive / Positive by Method)**			
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**
Apparently Healthy	5746	5727	28	19	5739	11	7	2	0	0	0

	ADVIA Centaur CHIV Assay				FDA Approved HIV Ab Assay			Repeatedly Reactive Specimens (Number Reactive / Positive by Method)			
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**
Apparently Healthy Pregnant Prospective	157	157	0	0	157	0	0	NA[a]	NA	NA	NA
Apparently Healthy Pregnant Retrospective	97	97	0	0	97	0	0	NA	NA	NA	NA
Pediatric HIV Low-risk	110	110	0	0	110	0	0	NA	NA	NA	NA
Hospitalized	30	30	1	0	30	0	0	NA	NA	NA	NA
Total	6140	6121	29	19	6133	11	7	2	0	0	0
Total (%)		99.69	0.47	0.31	99.89	0.18	0.11	0.03	0	0	0

[a] NA = Not applicable

Table 7 summary: The specificity of the ADVIA Centaur CHIV assay in the low risk population was 99.72% with exact 95% confidence interval of 99.56% to 99.84%.

Results: The specificity of the ADVIA Centaur CHIV assay in the low risk population was 99.72% (= (6138 subjects – 17 CHIV repeatedly reactive subjects) / (6140 subjects – 2 confirmed positives) = 6121/6138) with exact 95% confidence interval of 99.56% to 99.84%. The results demonstrate acceptable performance.

Sensitivity

Reactivity in Individuals Known to be Positive for Antibodies to HIV-1

A multisite clinical study was performed to assess the sensitivity of the ADVIA Centaur CHIV assay in 942 individuals who were known to be infected with HIV-1. This population also includes patients on anti-retroviral therapy. Of the 942 HIV-1 known positive individuals, 355 individuals were HIV symptomatic for AIDS, 91 individuals were asymptomatic for AIDS, and 496 individuals were known positive for AIDS at study enrollment. All 942 specimens were repeatedly reactive using the ADVIA Centaur CHIV assay.

Results: The sensitivity for this population was 100.00% with an exact 95% confidence interval of 99.61% to 100.00%. The results demonstrate acceptable performance.

Table 8: Reactivity in Individuals Known to be Positive for Antibodies to HIV-1

	ADVIA Centaur CHIV Assay				FDA Approved HIV Ab Assay		
Specimen Category	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Symptomatic	355	0	355	355	0	355	355
Asymptomatic	91	0	91	91	0	91	91
Known Positive for AIDS	496	0	496	496	0	496	496
Total	942	0	942	942	0	942	942
Total (%)		0.0	100.0	100.0	0.0	100.0	100.0

Table 8 summary: The sensitivity was 100.00% with an exact 95% confidence interval of 99.61% to 100.00%.

Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

The sensitivity of the ADVIA Centaur CHIV assay was assessed in 201 individuals who were known to be infected with HIV-2. All 201 specimens were repeatedly reactive using the ADVIA Centaur CHIV assay.

Results: The sensitivity for this population was 100.00% with an exact 95% confidence interval of 98.18% to 100.00%. The results demonstrate acceptable performance.

Table 9: Reactivity in Individuals Known to be Positive for Antibodies to HIV-2

	ADVIA Centaur CHIV Assay				FDA Approved HIV Ab Assay		
Specimen Category	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Known Positive for HIV-2	201	0	201	201	0	201	201

Table 9 summary: All 201 samples tested were reactive with the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay.

Reactivity in Specimens Positive for Antibodies to HIV-1 Group O

The sensitivity of the ADVIA Centaur CHIV assay was assessed in 65 specimens, 15 of which were from individuals known to be positive for antibodies to HIV-1 Group O, and 50 of which were spiked/contrived Group O positive specimens. All 15 HIV-1 Group O specimens and the 50

spiked/contrived HIV-1 Group O specimens were repeatedly reactive using the ADVIA Centaur CHIV assay.

Results: The sensitivity for the 15 HIV-1 Group O specimens was 100.00% with an exact 95% confidence interval of 78.20% to 100.00%. The sensitivity for 50 spiked/contrived Group O specimens was 100.00% with an exact 95% confidence interval of 92.89% to 100.00%. The results demonstrate acceptable performance.

Table 10: Reactivity in Specimens Positive for Antibodies to HIV-1 Group O

	ADVIA Centaur CHIV Assay				FDA Approved HIV Ab Assay		
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Group O	15	0	15	15	0	15	15
Group O - contrived	50	0	50	50	0	50	50
Total	65	0	65	65	0	65	65
Total (%)		0.0	100.0	100.0	0.0	100.0	100.0

Table 10 summary: All Group O specimens tested were repeatedly reactive.

Reactivity in Specimens Reactive for HIV-1 p24 Antigen, Antibody Negative and Western Blot Negative

The sensitivity of the ADVIA Centaur CHIV assay was assessed in a total of 94 antigen positive, antibody negative, Western Blot negative specimens. Of these, 44 were authentic p24 Ag positive, HIV Ab negative specimens that consisted of 24 samples from seroconversion panels, 10 samples from p24 antigen Mixed Titer Panels, and 10 aliquots from individual donor units. Fifty (50) of the 94 specimens were contrived by spiking individual HIV negative specimens with aliquots of authentic p24 Ag positive, HIV Ab negative specimens. These specimens were tested with the ADVIA Centaur CHIV and the results are shown in Table 11 below.

Results: A total of 43 of the 44 authentic p24 Ag positive/Ab negative specimens were reactive using the ADVIA Centaur CHIV assay. The sensitivity for this population was 97.73% with an exact 95% confidence interval of 87.98% to 99.94%.

A total of 49 of the 50 contrived specimens were repeatedly reactive using the ADVIA Centaur CHIV assay. The sensitivity for this population was 98.00% with an exact 95% confidence interval of 89.35% to 99.95%.

Table 11: ADVIA Centaur CHIV Assay Reactivity with Specimens Reactive for HIV-1 p24 Antigen, Antibody Negative and Western Blot Negative

	ADVIA Centaur CHIV Assay			
Specimen Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
Authentic p24 Ag+/Ab- Specimens[a]	44	1	43	43
Contrived/Spiked Samples[b]	50	1	49	49
Total	94	2	92	92
Total (%)		2.13	97.87	97.87

[a] One mixed titer panel sample that was nonreactive for the ADVIA Centaur CHIV, was found to be reactive in two p24 Ag assays but was nonreactive in a third p24 Ag assay and in an RNA test.
[b] One contrived sample was found to be nonreactive when tested using the ADVIA Centaur CHIV assay. This contrived sample was targeted to be close to the clinical cut-off (1.00 Index) but due to sample imprecision around the cut-off, the recovered value, 0.95 Index, was close to but slightly less than the cut-off Index.

Table 11 summary: A total of 43 of the 44 authentic p24 Ag positive/Ab negative specimens and 49 of the 50 contrived specimens were reactive using the ADVIA Centaur CHIV assay.

Reactivity in Samples from High Risk Individuals

A total of 1100 specimens (1077 prospective and 23 retrospective specimens) were tested. Of the 1100 specimens at high risk for HIV-1 infection, there were 401 specimens from pregnant females, 204 pediatric specimens, and 495 specimens from other individuals at high risk for HIV-1. The specimens were collected from individuals ranging in age from 4 months to 79 years.

Results: Of the 1100 specimens tested with the ADVIA Centaur CHIV assay, 2.91% (32/1100) were repeatedly reactive of which 75.00% (24/32) were confirmed positive by HIV-1 Western Blot, HIV-2 EIA, or HIV-1 RNA testing. Of the 1100 specimens tested with the FDA approved HIV Ab assay assay, 2.55% (28/1100) were repeatedly reactive and 24 of these 28 specimens, or 85.71% (24/28) were confirmed positive by HIV-1 Western Blot, HIV-2 EIA, or HIV-1 RNA testing. Four specimens were nonreactive by HIV-1 WB, HIV-2 EIA, HIV-1 p24Ag, and HIV-1 RNA PCR. None of the specimens that were repeatedly reactive only on the ADVIA Centaur CHIV assay were confirmed positive.

Table 12: ADVIA Centaur CHIV Assay Reactivity with Samples from High Risk Individuals

		ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay			Repeatedly Reactive Specimens (Number Reactive / Positive by Method)			
Specimen Category	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 antigen**	**HIV-1 RNA PCR**
Illicit Injection	47	47	0	0	47	0	0	NA[a]	NA	NA	NA
MSM	32	31	1	1	32	0	0	0	0	0	0
Multiple Transfusions	40	40	0	0	40	0	0	NA	NA	NA	NA
Renal dialysis	27	27	1	0	27	0	0	NA	NA	NA	NA
STD	108	108	0	0	108	0	0	NA	NA	NA	NA
Other	216	209	7	7	212	4	4	1	0	0	1
Hemophiliac-Prospective	2	2	0	0	2	0	0	NA	NA	NA	NA
Hemophiliac-Retrospective	23	23	0	0	23	0	0	NA	NA	NA	NA
Pregnant	401	379	23	22	379	22	22	18	2[b]	0	0
Pediatric	204	202	2	2	202	2	2	2	NA	NA	NA
Total	1100	1068	34	32	1072	28	28	21	2	0	1
Total %		97.09	3.09	2.91	97.50	2.55	2.55	1.91	0.18	0.00	0.09

[a] NA = Not applicable
[b] Confirmed by HIV-2 Western Blot

Table 12 summary: 32 specimens were repeatedly reactive with the ADVIA Centaur CHIV assay and 28 specimens were repeatedly reactive with the FDA approved HIV Ab assay. 24 specimens that were repeatedly reactive with the ADVIA Centaur CHIV assay were confirmed positive by Western Blot, HIV-2 EIA or HIV-1 RNA testing

Table 13: ADVIA Centaur CHIV Assay Versus FDA Approved HIV Ab Assay Reactivity

ADVIA Centaur CHIV Assay	**FDA Approved HIV Ab Assay**		
	Repeatedly Reactive	**Nonreactive**	**Total**
Repeatedly Reactive	28	4[a]	32
Nonreactive	0	1068	1068
Total	28	1072	1100

[a] Four specimens were nonreactive by HIV-1 WB, HIV-2 EIA, HIV-1 p24 Ag, and HIV-1 RNA PCR.

Table 13 summary: 32 specimens were found to be repeatedly reactive by the ADVIA Centaur CHIV assay and 28 specimens were found to be repeatedly reactive with the FDA approved HIV Ab assay.

Reactivity in Individuals from an HIV-2 Endemic Region

Individuals at high risk of HIV-2 infection included 501 prospectively enrolled from Guinea-Bissau, an HIV-2 endemic area. The specimens were tested by the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay.

Results: of the 501 specimens tested, a total of 26 samples were repeatedly reactive with both the ADVIA Centaur CHIV assay and FDA approved HIV Ab assay. One (1) specimen was repeatedly reactive for the FDA approved HIV Ab assay only, and 2 specimens were repeatedly reactive for the ADVIA Centaur CHIV assay only. Of the 26 samples that were found to be repeatedly reactive for both assays, 25 samples were confirmed positive using one or more confirmatory tests. All 25 confirmed positive samples were found to be repeatedly reactive by the ADVIA Centaur CHIV and FDA approved HIV Ab assay. Twenty three (23) specimens repeatedly reactive using the ADVIA Centaur CHIV assay were confirmed positive by Western Blot. Two (2) specimens repeatedly reactive using the ADVIA Centaur CHIV assay were confirmed positive by HIV-2 ABS (EIA). One specimen that was found to be nonreactive for the ADVIA Centaur CHIV assay and repeatedly reactive for the FDA approved HIV Ab assay was found to be nonreactive for the HIV-2 EIA confirmatory assay. Two specimens that were found to be repeatedly reactive for the ADVIA Centaur CHIV assay and nonreactive for the FDA approved HIV Ab assay were found to be nonreactive for the HIV-2 EIA confirmatory assay.

Table 14: Reactivity in Individuals From an HIV-2 Endemic Region

		ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay			Number Reactive / Positive by Method			
Specimen	**Number tested**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**
HIV-2 Endemic Area	501	473	29	28	474	27	27	23	2[a]	0	0
Total %		94.41	5.79	5.59	94.60	5.39	5.39	4.59	0.40	0	0

[a] Confirmed by HIV-2 Western Blot

Table 14 summary: 28 specimens were found to be repeatedly reactive by the ADVIA Centaur CHIV assay and 27 specimens were found to be repeatedly reactive with the FDA approved HIV Ab assay.

Table 15: Reactivity in Individuals from an HIV-2 Endemic Region – Comparison of ADVIA Centaur CHIV Assay versus the FDA Approved HIV Ab Assay

ADVIA Centaur CHIV Assay	FDA Approved HIV Ab Assay		
	Repeatedly Reactive	**Nonreactive**	**Total**
Repeatedly Reactive	26	2[a]	28
Nonreactive	1[b]	472	473
Total	27	474	501

[a] Two specimens were nonreactive by HIV-1 Western Blot, HIV-2 EIA, HIV-1 p24 Ag, and HIV-1 RNA PCR.
[b] One specimen was nonreactive by HIV-1 Western Blot, HIV-2 EIA, HIV-1 p24 Ag, and HIV-1 RNA PCR.

Table 15 summary: Of the 29 specimens repeatedly reactive on the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay, 26 specimens were repeatedly reactive for both assays, 1 was repeatedly reactive for FDA approved HIV Ab assay only, and 2 were only repeatedly reactive for the ADVIA Centaur CHIV assay.

Pregnancy Population Studies

A multisite clinical study was performed to compare the performance of the ADVIA Centaur CHIV assay to the FDA approved HIV Ab assay using specimens from pregnant females. Prospectively and retrospectively collected samples from 718 pregnant women across all three trimesters were tested at three testing sites.

Results: All 63 HIV positive pregnant female specimens were repeatedly reactive by the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay. The sensitivity for this population was 100.00% (63/63) with an exact 95% confidence interval of 94.31% to 100.00%.

Of the 401 high risk pregnant female specimens tested, 22 were found to be repeatedly reactive for both the ADVIA Centaur CHIV and the FDA approved HIV Ab assays. From the 22 samples, 20 were confirmed positive by HIV confirmatory testing. The ADVIA Centaur CHIV assay identified 20 newly infected pregnant female specimens from this population. A total of 633 low and high risk pregnant female specimens were nonreactive by the ADVIA Centaur CHIV assay. The specificity by the ADVIA Centaur CHIV assay for the low risk pregnant female population was 100.00% (254/254) with an exact 95% confidence interval of 98.51% to 100.00%.

Table 16: Reactivity of the ADVIA Centaur CHIV Assay in Pregnant Females

		ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay			Number Reactive / Positive by Method			
Specimen category	**Number tested**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**HIV-1 Western Blot**	**HIV-2 EIA**	**HIV-1 p24 Ag**	**HIV-1 RNA PCR**
HIV-Positive pregnant Females	63	0	63	63	0	63	63	NA[a]	NA	NA	NA
High-Risk Pregnant Females	401	379	23	22	379	22	22	18	2[b]	0	0
Apparently Healthy Pregnant (Prospective)	157	157	0	0	157	0	0	NA	NA	NA	NA
Apparently Healthy Pregnant (Retrospective)	97	97	0	0	97	0	0	NA	NA	NA	NA
Total	718	633	86	85	633	85	85	18	2	0	0
Total %		88.16	11.98	11.84	88.16	11.84	11.84	2.51	0.28	0	0

[a] NA = Not applicable

[b] Confirmed by HIV-2 Western Blot

Table 16 summary: All 63 HIV positive pregnant female specimens were repeatedly reactive by the ADVIA Centaur CHIV assay and the FDA Approved HIV Ab assay. All 254 low risk pregnant female specimens were nonreactive by the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay. Of the 401 high risk pregnant female specimens tested, 22 were found to be repeatedly reactive for both the ADVIA Centaur CHIV and the FDA approved HIV Ab assays.

Table 17: Reactivity of the Pregnant Females at High Risk for Infection with HIV

		ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay		
Population	**Number Tested**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**	**Non-reactive**	**Initially Reactive**	**Repeatedly Reactive**
First Trimester	57	51	6	6	51	6	6
Second Trimester	98	96	2	2	96	2	2
Third Trimester	246	232	15	14	232	14	14
Total	401	379	23	22	379	22	22
Total (%)		94.51	5.74	5.49	94.51	5.49	5.49

Table17 summary: Of the 401 high risk pregnant female specimens tested, 22 were found to be repeatedly reactive for both the ADVIA Centaur CHIV and the FDA approved HIV Ab assays.

Pediatric Populations (2 - 21 years)
A multisite clinical study was performed to compare the performance of the ADVIA Centaur CHIV assay to the FDA approved HIV Ab assay using pediatric specimens. A total of 364 pediatric specimens that were tested across three sites included both prospective as well as vendor supplied retrospective samples. The pediatric samples included 110 low risk, 204 high risk and 50 HIV reactive samples. The prospective and retrospective samples were collected from children in the age range from 2 to 21 years of age. Repeatedly reactive low risk and high risk samples were tested by HIV confirmatory testing.

Results: All 50 HIV reactive specimens were repeatedly reactive by the ADVIA Centaur CHIV assay and were confirmed positive by the HIV-1 Western Blot confirmatory test. The sensitivity for both the prospective and retrospective populations was 100.00%.

A total of 312 of the 314 low and high risk pediatric specimens were nonreactive by the ADVIA Centaur CHIV assay. Two high risk specimens that were repeatedly reactive by the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay were confirmed to be reactive by HIV-1 Western Blot. The ADVIA Centaur CHIV assay identified two newly infected pediatric specimens from the high risk population. The specificity by the ADVIA Centaur CHIV assay for the low pediatric population was 100% (110/110) with an exact 95% confidence interval of 96.63% to 100.00%.

Table 18: The Reactivity of the ADVIA Centaur CHIV Assay with Pediatric Samples

		ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay			Number Reactive / Positive by Method
Specimen category	**Number tested**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**HIV-1 Western Blot**
Pediatric HIV Low Risk	110	110	0	0	110	0	0	NA[a]
Pediatric High-Risk	204	202	2	2	202	2	2	2
Pediatric HIV Positive Prospective	15	0	15	15	0	15	15	NA
Pediatric HIV Positive Retrospective	35	0	35	35	0	35	35	NA
Total	364	312	52	52	312	52	52	2
Total %		85.71	14.29	14.29	85.71	14.29	14.29	0.55

[a] NA = Not applicable

Table 18 summary: All 50 (35 + 15) HIV reactive specimens were repeatedly reactive by the ADVIA Centaur CHIV assay and were confirmed positive by the HIV-1 Western Blot confirmatory test. 312 of the 314 low and high risk pediatric specimens (110 + 204) were nonreactive by the ADVIA Centaur CHIV assay.

Table 19: Distribution of High Risk Pediatric Specimens Categorized by Age Range and Gender

			ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay			Number Reactive / Positive by Method
Age	**Gender**	**Number tested**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**HIV-1 Western Blot**
2 to 5 years	Female	7	7	0	0	7	0	0	NA[a]
	Male	10	10	0	0	10	0	0	NA
6 to 10 years	Female	34	34	0	0	34	0	0	NA
	Male	27	27	0	0	27	0	0	NA
11 to 15 years	Female	44	43	1	1	43	1	1	1
	Male	27	27	0	0	27	0	0	NA
16 to 21 years	Female	27	26	1	1	26	1	1	1
	Male	28	28	0	0	28	0	0	NA

			ADVIA Centaur CHIV assay			FDA Approved HIV Ab Assay			Number Reactive / Positive by Method
Age	**Gender**	**Number tested**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**Non-reactive**	**Initially reactive**	**Repeatedly reactive**	**HIV-1 Western Blot**
Total		204	202	2	2	202	2	2	2
Total %			99.02	0.98	0.98	99.02	0.98	0.98	0.98

[a] NA = Not applicable

Table 19 summary: 202 out of the 204 high risk pediatric specimens were nonreactive by the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay. Two (2) high risk specimens that were repeatedly reactive by the ADVIA Centaur CHIV assay and the FDA approved HIV Ab assay were confirmed to be reactive by HIV-1 Western Blot.

XI. Inspections

Manufacturing Facilities Review/Inspection

Siemens Healthcare Diagnostics, Inc. (FEI #1219913) has recently been inspected (2/1/2013 – 2/20/2013). The FY13 assignment (FACTS 1426960) comprised enforcement of medical device reporting (MDR) regulations, 2 post market audit inspections, and a for-cause inspection. The most recent inspection noted above was classified as No Action Indicated (NAI).

Based on the information provided in the PMA submission, and the previous inspection reports supporting the overall compliance status of the applicant holder, the review committee recommended waiving the pre-approval inspection for the facility associated with this PMA.

Bioresearch Monitoring (BIMO) Inspections

CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments at the three testing sites in the United States. These inspections did not reveal significant problems that impact the data submitted in this PMA. The inspections were classified as No Action Indicated (NAI).

XII. Conclusions Drawn from the Studies

Risk/Benefit Analysis

As a diagnostic test, the ADVIA Centaur® HIV Ag/Ab Combo assay involves removal of blood from an individual for testing purposes. This test presents no more of a safety hazard to an individual than is presented to an individual who is having their blood drawn for any other diagnostic evaluation. The benefit to HIV-1 or HIV-2 infected individuals tested by this assay outweighs any potential adverse event or risk to the patient or user due to assay malfunction or operator error. The potential risks encountered with this in vitro diagnostic test are not unusual in the clinical laboratory setting. Appropriate warnings for these risks are contained in the labeling and package inserts for these devices. Standard good laboratory

practices are considered sufficient to mitigate the risks to the end user. Potential adverse effects of the ADVIA Centaur® HIV Ag/Ab Combo (CHIV) assay relate to the risk of false positive and false negative results. While performance studies indicate that this risk is likely to be very small, the potential for inaccurate results exists. The risk of incorrect results is minimized by following the procedures and instructions outlined in the Package Insert.

Safety and Effectiveness

Multi-centered clinical studies were conducted in the US. The ADVIA Centaur® HIV Ag/Ab Combo (CHIV) Assay performed with clinical sensitivity and specificity comparable to a commercially available FDA approved HIV Ab assay. The results from the clinical studies indicate that the ADVIA Centaur® HIV Ag/Ab Combo assay, together with supplemental testing, can be used safely and effectively for the qualitative in vitro detection of HIV-1 p24 antigen, HIV-1 antibody, HIV-2 antibody and HIV-1 Group O antibody in human serum. Reactive specimens must be investigated by additional, more specific, or supplemental tests. Both confirmation of the test result on a freshly drawn sample and counseling are considered an important part of testing for HIV antigen and antibody to HIV-1 and HIV-2. A negative test result at any point in the investigation of individual subjects does not preclude the possibility of exposure to or infection with HIV-1 and/or HIV-2. Negative results can occur if the quantity of marker present in the sample is below the detection limit of the assay, or if the marker is not present during the stage of disease in which a sample is collected.

The safety and effectiveness of the ADVIA Centaur ® HIV Ag/Ab Combo assay has been shown in the clinical and non-clinical studies performed. The assay has been shown to be an effective tool in detecting infection with HIV-1 or HIV-2.