SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hepatitis B Surface Antigen
Hepatitis B Surface Antigen Confirmatory
Hepatitis B Surface Antigen Positive and Negative Control Materials

Device Trade Name: ADVIA Centaur® HBsAgII
ADVIA Centaur® HBsAg Confirmatory
ADVIA Centaur® HBsAg Quality Control Material

Device Procode: LOM

Applicant's Name and Address:
Siemens Healthcare Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591

Dates of Panel Recommendation: Not applicable

Premarket Approval Application (PMA) Number: P110041

Date of FDA Notice of Approval: June 6, 2013

II. INDICATIONS FOR USE

1. ADVIA Centaur HBsAgII

The ADVIA Centaur HBsAgII (HBsII) assay is an *in vitro* immunoassay for the qualitative detection of hepatitis B surface antigen (HBsAg) in human adult, adolescent, and pediatric serum and plasma (EDTA, lithium-heparin, or sodium-heparin), and neonatal samples using the ADVIA Centaur and ADVIA Centaur XP systems. The assay may be used in conjunction with other serological and clinical information to diagnose individuals with acute or chronic hepatitis B infection. The assay may also be used to screen for hepatitis B infection in pregnant women to identify neonates who are at risk of acquiring hepatitis B during the perinatal period.

WARNING
United States federal law restricts this device to sale by or on the order of a physician. This assay has not been FDA-cleared or approved for the screening of blood or plasma donors.

2. ADVIA Centaur HBsAg Confirmatory

The ADVIA Centaur HBsAg Confirmatory assay is an *in vitro* immunoassay for the confirmation of hepatitis B surface antigen (HBsAg) in human serum and plasma (potassium EDTA, lithium-heparin, or sodium-heparin), and neonatal samples using the ADVIA Centaur and ADVIA Centaur XP systems. The assay is intended to be used to confirm the presence of HBsAg in samples that are repeatedly reactive using the ADVIA Centaur HBsAgII assay.

WARNING
United States federal law restricts this device to sale by or on the order of a physician. This assay has not been FDA-cleared or approved for the screening of blood or plasma donors.

3. ADVIA Centaur HBsAg Quality Control Material

For monitoring the performance of the HBsAg, HBsAgII and HBsAg Confirmatory assays on the ADVIA Centaur systems. The performance of the HBsAg quality control material has not been established with any other HBsAg or HBsAg Confirmatory assays.

United States federal law restricts this device to sale by or on the order of a physician.

III. CONTRAINDICATIONS

None.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ADVIA Centaur HBsAgII, the ADVIA Centaur HBsAg Confirmatory, and the ADVIA Centaur HBsAg Quality Control Material labeling.

V. DEVICE DESCRIPTION

Kit Configurations and Components

The ADVIA Centaur HBsAgII kit is comprised of the following components:

ADVIA Centaur HBsAgII ReadyPack primary reagent pack:

- Solid Phase - 21.0 mL/ reagent pack. Streptavidin-coated magnetic latex particles (60 mg/dL) in buffer with bovine serum albumin, bovine gamma globulin, goat serum, surfactant, sodium azide (< 0.1%) and preservatives
- Lite Reagent - 8.0 mL/ reagent pack. Acridinium ester-labeled monoclonal mouse anti-HBsAg (~0.6 µg/mL) in buffer with bovine serum albumin, bovine gamma globulin, goat serum, mouse IgG, surfactant, sodium azide (< 0.1%) and preservatives

ADVIA Centaur HBsAgII ReadyPack ancillary reagent pack;

- Ancillary Pack Reagent - 25.0 mL/ reagent pack. Biotinylated monoclonal mouse anti-HBsAg antibodies (~2.0 μg/mL) and acridinium ester-labeled monoclonal mouse anti-HBsAg (~0.3 μg/mL) in buffer with bovine serum albumin, bovine gamma globulin, goat serum, mouse IgG, surfactant, sodium azide (< 0.1%) and preservatives

ADVIA Centaur HBsAgII Calibrators:

- Low Calibrator – 2 x 2.5 mL
- High Calibrator – 2 x 2.5 mL

ADVIA Centaur HBsAgII Master Curve card

ADVIA Centaur HBsAgII Calibrator Assigned Value cards

The ADVIA Centaur HBsAg Confirmatory kit is comprised of the following components:

ADVIA Centaur HBsAg Confirmatory ReadyPack ancillary reagent pack:

- Reagent A – 5.0 mL/ reagent pack. Neutralizing Reagent – human plasma positive for antibodies to HBsAg with sodium azide (<0.1%).
- Reagent B – 5.0 mL/ reagent pack. Non-Neutralizing Control. Reagent – human plasma negative for antibodies to HBsAg with sodium azide (<0.1%).

The ADVIA Centaur HBsAg Quality Control Material contains:

- Negative Control – 2 vials with 10.0 mL/vial. Recalcified human plasma
- Positive Control – 2 vials with 10.0 mL/vial. Recalcified human plasma

Assay Principle and Format

ADVIA Centaur HBsAgII:
The ADVIA Centaur HBsAgII assay is a sandwich immunoassay using direct, chemiluminometric technology. The Ancillary Pack Reagent containing biotinylated anti-HBs mouse monoclonal capture antibodies and an acridinium-ester-labeled anti-HBs mouse monoclonal antibody is added to the sample.

The HBsAg in the sample forms complexes with the antibodies. A second acridinium-ester-labeled anti-HBs mouse monoclonal antibody (Lite Reagent) is added from the primary reagent pack. Streptavidin-coated magnetic latex particles in the Solid Phase capture the HBsAg-antibody complexes. The sample is incubated with Ancillary Pack Reagent, and then with Solid Phase and Lite Reagent. Antibody-antigen complexes will form if hepatitis B surface antigen is present in the sample.

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

- dispenses 100 μL of sample into a cuvette
- dispenses 60 μL of Ancillary Pack Reagent and incubates for 5 minutes at 37°C

- dispenses 105 µL of Solid Phase and 40 µL of Lite Reagent and incubates the mixture 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 or in the online help system

A direct relationship exists between the amount of HBsAg activity present in the patient sample and the amount of relative light units (RLUs) detected by the system. A result of Reactive or Nonreactive is determined according to a cutoff of 1.0 Index Value established with the calibrators.

ADVIA Centaur HBsAg Confirmatory:
The ADVIA Centaur HBsAg Confirmatory assay is based on the principle of specific antibody neutralization. A patient sample that has tested repeatedly reactive for HBsAg is incubated with polyclonal (human) antibody to HBsAg. The polyclonal antibody will bind to HBsAg present in the sample thereby neutralizing the antigen. The neutralized HBsAg is blocked from binding to the monoclonal antibodies in the ADVIA Centaur HBsAgII assay; this blocking of the HBsAg results in a reduction of signal when compared to a second aliquot of sample that has been incubated with a non-neutralizing control reagent. The non-neutralizing control reagent serves as a control for the neutralization as well as the zero percent baseline for calculation of the amount of reduction in signal as percent neutralization. A sample is considered positive for HBsAg if the percent neutralization is 50% or greater after treatment with the polyclonal antibody (Neutralizing Reagent).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The patient's medical history and thorough physical examination, in addition to hepatitis serology, determination of liver enzyme levels, and biopsy of the liver, will provide further information on the status of a hepatitis B viral infection.

Alternative procedures for the detection of HBV in patients depend on the detection of HBV deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) assays or nucleic acid testing (NAT), or the detection of HBV antigens and antibodies by commercially available assays that are licensed or approved in the United States (US).

VII. MARKETING HISTORY

The ADVIA Centaur HBsAgII assay, ADVIA Centaur HBsAg Confirmatory, and the ADVIA Centaur HBsAg Quality Control Material are marketed in the following countries:

Australia	Brazil	Canada
Egypt	Austria	Belgium
Bulgaria	Cyprus	Czech Republic
Denmark	Estonia	Finland
France	Germany	Greece
Hungary	Ireland	Italy
Latvia	Lithuania	Luxembourg
Malta	Netherlands	Poland
Portugal	Romania	Slovakia
Slovenia	Spain	Sweden
United Kingdom	Hong Kong	India
Indonesia	Israel	Japan
Korea	Malaysia	New Zealand
Philippines	Singapore	South Africa
Thailand	UAE	Uruguay
Vietnam		

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

When used according to the instructions in the package insert, there are no known direct adverse effects of this device on the health of the user. Failure of the test to perform as indicated or human error during performance of the test may lead to a false diagnosis and improper patient management. Below is a list of the potential adverse effects associated with the use of the ADVIA Centaur HBsAgII assay, ADVIA Centaur HBsAg Confirmatory, and the ADVIA Centaur HBsAg Quality Control Material:

- Failure of the device to perform as indicated or human error in use of the device may lead to a false result.
- A false positive result using an HBsAg assay is not considered a patient or public health concern as a positive result in a clinical lab setting is usually followed up with supplemental testing. Either additional HBV marker testing is performed or an HBsAg positive result is confirmed by neutralization. An exception to this is using HBsAg tests to screen pregnant women for the presence of HBsAg. This testing helps to determine if a neonate is at high risk of acquiring HBV during the prenatal period.
- Pregnant women are tested during an early prenatal visit. If they are HBsAg nonreactive during this testing, and at high risk for HBV infection, they are re-tested during the third trimester. If the result is positive, it is recommended that hepatitis immune globulin (HBIG) and vaccine be provided to the newborn within 12 hours of birth. If an assay is false positive and the newborn receives HBIG, the newborn would be exposed to the risks of receiving a human source product.
- The risks of a false negative result in a diagnostic setting are highest when testing pregnant women because HBsAg may be the only marker used. If the result is negative, then the child is vaccinated within 2 months of birth. If the result is incorrect (false negative), then the neonate is at a higher risk of acute and chronic HBV infection, since HBIG and vaccine would not be provided within 12 hours of birth.

- From time to time, false negative results due to gene mutation have been reported for the HBsAg assays produced by a number of different manufacturers. Because of the complexity of the mutations that can occur, no manufacturer can guarantee to detect all patients.
- A false positive result using an HBsAg confirmatory neutralization procedure is not considered a patient or public health concern because in order for a false positive to occur, the control sample (non-neutralized result) and the percent neutralization (in the neutralized tube) would both have to be incorrect for a reported false positive result. If this situation were to occur, the implications would be the same as described for false positive results for HBsAg assays
- A false negative result using an HBsAg confirmatory neutralization procedure could occur if the neutralized sample result were incorrect either due to a falsely increased signal with the neutralized sample, or due to some other malfunction, laboratory or technician error when assayed. A falsely increased signal could be interpreted as a failure to neutralize. If this situation were to occur, the implications would be the same as described for false negative results for HBsAg.

IX. SUMMARY OF NONCLINICAL LABORATORY STUDIES

Nonclinical studies were performed at Siemens Healthcare Diagnostics to evaluate the performance characteristics of the ADVIA Centaur HBsAgII and the ADVIA Centaur HBsAg Confirmatory assays. The studies are described below.

Analytical Sensitivity using the PEI HBsAg Reference Material

To examine the analytical sensitivity of the ADVIA Centaur HBsAgII assay a dilution series of HBsAg (Ay and Ad) (100 PEI U/mL) standard using negative plasma basepool was tested using two lots of ADVIA Centaur HBsAgII reagents. Index values were obtained by 2-point calibration.

The HBsAg ay subtype concentration at cut-off (1.0 Index), estimated from the linear regression analysis was 0.031 PEI U/mL with both reagent lots tested.

The HBsAg ad subtype concentration at cut-off (1.0 Index), estimated from the linear regression analysis was 0.014 & 0.017 PEI U/mL with pilot lots 1 and 3 respectively on the ADVIA Centaur system.

Analytical Sensitivity using the WHO Standard

The analytical sensitivity of the ADVIA Centaur HBsAgII assay was evaluated using dilutions of the HBsAg WHO International Standard assayed as unknowns on two reagent lots. The WHO 2nd Standard was diluted with negative plasma basepool from 1:100 out to 1:10,000. Theoretical values for these subsequent dilutions were calculated using the dilution factor. The calculated analytical sensitivity as determined by linear regression analysis on the ADVIA Centaur system with the WHO 2nd standard was 0.041, and 0.035 IU/mL for two lots of ADVIA Centaur HBsAgII assay.

Potentially Cross Reactive Samples

The ADVIA Centaur HBsAgII assay was evaluated for potential cross-reactivity with other viral infections and disease state specimens. The reactive HBsAg status of each

specimen was verified using an HBsAg reference assay. The following results were obtained using the ADVIA Centaur HBsAgII assay:

Sample Type	Number Tested	No. Positive
Rubella	10	0
VZV	10	0
SLE	10	0
ANA	10	0
EBV	10	0
HSV-1	10	0
Anti-HBcT	10	4*
Anti-HCV	10	0
Anti-HIV	10	0
Anti-HAV	10	0
Anti-CMV IgM	10	0
Anti-CMV IgG	10	0
Flu Vaccine Recipient	10	0
Toxoplasma	10	0
HAMA	82	0
Rheumatoid Factor	53	0
Syphilis	10	0
Anti-HTLV I/II	10	0
Non-Viral Liver Disease	10	0
Total Tested	305	4*

*Confirmed positive with the ADVIA Centaur HBsAg Confirmatory

Endogenous Interfering Substances

The ADVIA Centaur HBsAgII assay was evaluated for interference due to high levels of endogenous substances following the guidelines described by the Clinical and Laboratory Standards Institute (CLSI) protocol EP7-A2. The following endogenous substances were evaluated for their potential effect on the ADVIA Centaur HBsAgII assay by measuring recovery from spiked patient samples across four sample matrices: serum, EDTA, lithium heparin, and sodium heparin plasma.

The mean percent-interference over all matrices was <10% with no change in the assay clinical interpretation for the following endogenous substances:
Conjugated Bilirubin at 40 mg/dL
Un-conjugated Bilirubin at 40 mg/dL
Cholesterol at 400 mg/dL
Hemogloblin at 500 mg/dL
Triglycerides at 1000 mg/dL
Human IgG at 6 g/dL
Human Serum Albumin at 12 g/dL and at 4g/dL
Biotin at 10ng/mL

Precision

Precision was evaluated according to the Clinical and Laboratory Standards Institute protocol EP5-A2. Samples were assayed in two replicates twice a day for 20 days. The

following results were obtained at Siemens Healthcare Diagnostics on two ADVIA Centaur instruments on two reagent lots.

			Within Run		Among Run		Among Date		Among Lot		Total	
Sample	**N**	**Mean**	**SD**	**CV(%)**	**SD**	**CV(%)**	**SD**	**CV(%)**	**SD**	**CV(%)**	**SD**	**CV(%)**
Positive Control	162	4.04	0.12	3.0	0.07	1.7	0.11	2.8	0.07	1.8	0.19	4.8
Serum 1	160	0.64	0.06	9.0	0.04	5.6	0.03	4.4	0	0	0.07	11.5
Serum 2	160	1.34	0.05	4.1	0.05	3.7	0.04	3.0	0.02	1.4	0.09	6.4
Serum 3	160	19.08	0.33	1.8	0.30	1.6	0.46	2.4	0	0	0.64	3.3
Serum 4	160	209.52	2.82	1.3	3.86	1.8	4.17	2.0	7.75	3.7	10.01	4.8
Serum 5	160	700.61	10.83	1.5	13.05	1.9	10.73	1.5	20.73	3.0	28.86	4.1
K2 EDTA 1	160	0.70	0.05	7.7	0.04	5.7	0.04	5.9	0.02	3.5	0.08	11.7
K2 EDTA 2	160	1.21	0.06	4.8	0.07	6.1	0	0	0.05	3.9	0.11	8.7
K2 EDTA 3	160	18.29	0.32	1.8	0.76	4.2	0.34	1.9	0	0	0.90	4.9
K2 EDTA 4	160	202.82	3.53	1.7	8.48	4.2	3.56	1.8	6.45	3.2	11.77	5.8
K2 EDTA 5	160	682.39	10.83	1.6	26.90	3.9	14.54	2.1	16.00	2.3	36.17	5.3
Lithium heparin 1	160	0.77	0.06	7.6	0.03	3.9	0.04	5.7	0	0	0.08	10.3
Lithium heparin 2	160	1.25	0.06	4.8	0.04	3.1	0.04	3.5	0	0	0.08	6.7
Lithium heparin 3	160	19.64	0.37	1.9	0.46	2.3	0.29	1.5	0.26	1.3	0.71	3.6
Lithium heparin 4	160	205.34	3.17	1.5	4.05	2.0	3.26	1.6	9.53	4.6	11.31	5.5
Lithium heparin 5	160	677.41	10.84	1.6	11.10	1.6	10.97	1.6	24.70	3.6	31.16	4.6
Sodium heparin 1	160	0.80	0.05	6.3	0.05	5.8	0.03	3.9	0.01	1.9	0.08	9.6
Sodium heparin 2	160	1.30	0.07	5.5	0.06	5.0	0.01	0.9	0.02	1.4	0.10	7.6
Sodium heparin 3	160	17.76	0.32	1.8	0.35	2.0	0.31	1.8	0.09	0.5	0.57	3.2
Sodium heparin 4	160	198.61	2.91	1.5	4.33	2.2	3.28	1.7	8.29	4.2	10.33	5.2
Sodium heparin 5	160	660.51	11.05	1.7	12.81	1.9	12.62	1.9	20.95	3.2	29.74	4.5

Effects of Type of Collection Tube on Matrix Data

The effects of the type of collection tube and different anticoagulants on assay performance were evaluated by testing human samples collected in different collection tubes, specifically; serum, EDTA (plasma), sodium heparin (plasma), and lithium heparin (plasma).

Blood was collected from 50 individual subjects. All samples were initially screened to be HBsAg negative. The same individuals were also screened for any levels of aHBs. Any donors >/= 10.0 index were used as negative samples for this study.

Negative specimens were spiked with a high titer HBsAg plasma pool to reach HBsAg target indexes covering low positive (2-8 index) and high positive (40-60 index) samples. The distribution of samples included in this study was 25 negatives, 13 low positives and 12 high positives. Calibration was 2-point using the lot specific calibrators.

Results: Clinical interpretation remained the same across all matrices. The average recovery for each tube type was within ±10% relative to serum.

Sample Handling Studies

A series of studies was conducted to evaluate various storage conditions and environmental stresses on human samples collected in the matrices claimed as suitable for use with the ADVIA Centaur HBsAgII assay. Samples were subjected to freeze/thaw cycling and various temperature storage conditions, and then tested in comparison to a non-stressed control sample to determine the impact of the stress on assay accuracy. The sample handling studies described here evaluated the effect of the following patient sample-handling conditions on ADVIA Centaur HBsAgII Index Values:

Extended time onboard the ADVIA Centaur System
Extended time in refrigerated (2 -8°C) storage in primary container
Extended time in refrigerated (2 -8°C) storage in secondary container
Extended time at room temperature (25°C) storage
Extended time in freezer (–20°C) storage
Multiple freeze thaw (–20°C/2- 8°C) cycles

Samples were collected from healthy subjects in serum and plasma collection tubes with a variety of anti-coagulants. Samples were spiked with HBsAg, aliquoted, and placed in various storage/stress conditions on the day of collection. Four samples were left unspiked. A baseline Index Value for each sample was established by testing with the ADVIA Centaur HBsAgII assay on the day of collection. All percentage recoveries were calculated against the baseline (day 0) value. Results from the sample-handling studies support the claims that samples can be subjected to the following conditions:

1. Samples can be kept onboard the ADVIA Centaur system for at least 24 hours
2. Samples can be stored at room temperature for 7 days
3. Samples can be stored refrigerated (2-8ºC) up to 14 days in primary container
4. Samples can be stored refrigerated (2-8ºC) up to 14 days in secondary container
5. Samples can be stored frozen (–20ºC) for long term storage (180 days tested)
6. Samples can be frozen and thawed up to 4 times

Sample Processing – Time to Centrifugation

This study was undertaken to determine the effect of time to centrifugation on the ADVIA Centaur HBsAgII assay Index Value. Blood was drawn from ten donors in each of the following tube types: Serum Red Top (plastic and glass) and K2-EDTA plasma.

Each sample was centrifuged within 0, 8 and 24 hours after draw and assayed.

No change in clinical interpretation was observed as a result of elapsed time between collection and centrifugation. All positive samples were within 10% of “0 Hour” sample Index Value after 8 hours and 24 hours before centrifugation.

Inversion of Gel Barrier Collection tubes

A sample-handling study was done to determine if inversion of barrier gel blood collection tubes interferes with ADVIA Centaur HBsAgII assay results. Blood samples were drawn from 10 in-house donors using separator / gel barrier blood collection tubes such as serum separator tube (SST). Sample tubes were spiked with different amounts of HBsAgII positive plasma. Four donor tubes were left unspiked. The tubes were inverted, centrifuged, and an aliquot was taken. The tubes were then inverted 5 times and another aliquot was taken. The 2 aliquots were compared in the ADVIA Centaur HBsAgII assay. A total of 5 inversions of the barrier gel collection tube had no effect on the HBsAgII Index Value for samples that were spiked with HBsAgII plasma and for unspiked samples.

Reagent, Calibrator, and Control Real Time Stability Studies

Real-time stability studies were carried out using three lots of Centaur HBsAgII, ADVIA Centaur HBsAg Confirmatory, and ADVIA Centaur HBsAg Quality Control Material. All kits and reagents were stored at the recommended storage temperature of 2 to 8ºC. Reagents and calibrators were evaluated at several checkpoints post manufacturing date.

The real time stability studies support a claim of 12 months of stability at 2-8ºC for the ADVIA Centaur HBsAgII assay, ADVIA Centaur HBsAg Confirmatory, and the ADVIA Centaur HBsAg Quality Control Material.

Reagent Onboard Stability (OBS) Studies

OBS studies were carried out on three lots of Centaur HBsAgII reagents on two ADVIA Centaur systems. Onboard stability testing occurred at several checkpoints after the reagents were placed onboard. A fresh pack served as the control for each time-point. A calibration interval of 21 days was evaluated using these results.

The OBS studies for the reagents supported 60 days OBS and a 21-day recalibration for the ADVIA Centaur HBsAgII and the ADVIA Centaur HBsAg Confirmatory assays.

Reagent Shipping Stability Studies

Shipping studies for the ADVIA Centaur HBsAgII assay demonstrated that the product tolerated 3 freeze/thaw cycles (-40ºC to 2-8ºC) with acceptable performance and without aggregation of the solid phase. Shipping studies also included cycling between 2-8°C to an elevated temperature (30°C). These studies also tested for shipment of upside-down packs. The recommended shipping conditions are to ship the reagents in an upright position and stored at 2 to 8ºC.

Calibrator and Control Open Vial Stability Studies

Studies were performed with the ADVIA Centaur HBsAgII assay calibrators and the ADVIA Centaur HBsAg Quality Control Material to evaluate the length of time the calibrator or control was stable once the vial was opened. Open vials were stored at the recommended storage conditions of 2 to 8ºC. The open vials were sampled periodically up to 92 days post initial opening. Fresh (unopened) vials were evaluated at each time point to serve as controls.

The acceptance criteria for this study was dose recovery within 15% (or 2 standard deviations) of the Index obtained using a fresh vial. The study supports an open vial use lifetime of up to 90 days.

Calibrator and Control Shipping Stability Studies

Shipping studies for the ADVIA Centaur HBsAgII assay calibrators and the ADVIA Centaur HBsAg Quality Control Material indicated that the products tolerated 3 freeze/thaw cycles (-20ºC to 2-8ºC and) with acceptable performance. Shipping studies also included 2-8°C to elevated temperature (37°C) cycling. The data demonstrate that calibrators and controls can perform according to specifications after freeze/thaw and heat stress. The recommended shipping conditions are to ship the ADVIA Centaur HBsAgII assay calibrators and the ADVIA Centaur HBsAg Quality Control Material in an upright position at 2-8ºC.

Microbiology Studies

The ADVIA Centaur HBsAgII reagents contain 0.01% Micr-o-protect and 0.009% Sodium Azide as preservatives to protect against adventitious contamination by microorganisms. Reagents were challenged in a study conducted according to USP requirements for Antimicrobial Effectiveness testing to assess the ability of the reagents to withstand or control microbial contamination. Reagents were inoculated with two pools of microbes containing the USP defined organisms. Results demonstrated that the preservative systems for reagents and calibrators met the USP requirements for antimicrobial effectiveness testing. No clinically significant changes in Index Values were observed after using inoculated reagents versus control reagents.

Instrument Studies

Environmental Testing

The purpose of the environmental testing was to assess ADVIA Centaur HBsAgII assay control recovery at the mean and extreme environmental conditions as specified in the ADVIA Centaur User's Guide. Each assay run was calibrated and performed on a single ADVIA Centaur system in an environmental chamber set at 18°C, 24°C and 30°C. The percent change in control recovery per degree is then calculated.

ADVIA Centaur HBsAgII assay environmental testing data met the specification of less than a 10% change in Index Value within a specified temperature shift for samples near the cutoff. The studies demonstrated acceptable performance of the ADVIA Centaur HBsAgII assay when performed on instruments operating at the extremes of the temperature range for the ADVIA Centaur system (18°C to 30°C).

Reagent Compatibility Testing

The purpose of this study was to confirm that there are no primary reagent interactions for assays that share the same reagent probe, and might therefore be susceptible to reagent carryover affects. Mitigation of any interference identified is accomplished

through Test Definition (TDef) scheduling options, using multiple water washes, or, on rare occasions, a Wash Pack with a solution other than water may be required.

The ADVIA Centaur HBsAgII assay was evaluated for its potential effect on all other assays that use the same reagent probe and, conversely, for the effect of all the other assay reagents that use the same reagent probe on the ADVIA Centaur HBsAgII assay. In this evaluation, for an interaction to be deemed acceptable and therefore not require mitigation, there must be <5% difference in Index Value between test and control, or no statistically significant change in Index Value.

In the submitted studies it was shown that the ADVIA Centaur HBsAgII Lite Reagent (LR) would interfere with the ADVIA Centaur TSTO Ancillary reagent. This interference is mitigated by the implementation of two washes with Ancillary Probe Wash 1 (APW1).

It was also demonstrated that the ADVIA Centaur Confirmatory Reagent A would interfere with the ADVIA Centaur HBsAgII Lite Reagent (LR). This interference is mitigated by the implementation of one wash with APW1.

Testing of Mutant samples on ADVIA Centaur HBsAgII

Twenty-five HBsAg positive mutant samples were tested using with the ADVIA Centaur HBsAgII assay. Panel members were prepared using recombinant DNA techniques to produce a series of HBsAg mutants. All sequences were evaluated by DNA sequence analysis to confirm the mutations. The recombinant mutants were expressed in insect cells using the baculovirus expression system. The cell lysates were analyzed using the ADVIA Centaur HBsAgII assay. One native mutant HBsAg plasma sample obtained from a positive patient specimen (S143L) was also included in the study. The performance of the ADVIA Centaur assay is shown in the following table:

Mutant Reactivity with ADVIA Centaur HBsAgII assay

HBsAg Mutant	Centaur Lot 109001
K122I	5.28
K122T	2.28
T123N	1.84
C124R	4.11
T126S	2.02
Q129H	1.93
G130D	2.11
T131N	4.11
M133L	1.76
F134H	4.29
F134N	7.44
C137W	5.00
T143L	2.09

HBsAg Mutant	Centaur Lot 109001
T143M	7.70
S143L (Native)	1.76
D144A	5.36
G145R	5.41
Y161H	3.08
K122N/G145R	4.51
T123N/G145R	2.71
M133I/F134H/D144V	1.38
T126S/Q129H/M133L	1.24
122RA123	3.05
122RG123	3.95
123RGT124	1.61

Conclusions Drawn from the Non Clinical Studies

The ADVIA Centaur HBsAgII assay was evaluated to demonstrate performance claims for cross-reactivity, interference, matrix type, specimen handling, and reagent stability. The results of the non-clinical studies, in conjunction with results of the clinical trial studies, support the intended use statement of the ADVIA Centaur HBsAgII assay.

X. SUMMARY OF CLINICAL STUDIES

Study Design

The safety and effectiveness of the ADVIA Centaur HBsAgII assay was determined by a clinical trial consisting of the following studies:

Reproducibility Study

Method reproducibility on the system was determined by testing an 8-member panel with the ADVIA Centaur HBsAgII assay. The panel consisted of two nonreactive serum samples (< 0.80 Index Value), two low reactive serum samples (1.0 –5.0 Index Value) and four reactive serum samples (25 – 1000 Index Value) along with low and high calibrators and positive and negative controls. Each sample was tested in replicates of four in each run and was assayed in two runs per day over at least five days at all three ADVIA Centaur testing sites. A total of three reagent lots were tested with all three lots used at each study site. Precision estimates for each reagent lot and site combination were calculated for Index Value units and for RLU units.

Assay Reproducibility Estimates across All Three Sites and All Three Reagent Lots

Sample Material	Number of				Mean HBsAgII Index	Within-Run		Between-Run		Between-Day		Between-Lot		Between-Site		Total	
	Lots	Sites	Days	Repli-cates		SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)
6412P	2	3	30	240	4.26	0.18	4.3	0.07	1.7	0.07	1.6	0.24	5.5	0.03	0.6	0.32	7.4
HBsIIR2	3	3	45	360	0.70	0.09	13.0	0.03	4.6	0.06	8.9	0.00	0.0	0.04	5.5	0.12	17.3
HBsIIR3	3	3	45	360	1.19	0.10	8.2	0.03	2.6	0.06	5.2	0.01	0.6	0.03	2.6	0.12	10.4
HBsIIR4	3	3	45	360	2.73	0.12	4.6	0.06	2.1	0.07	2.4	0.07	2.7	0.01	0.5	0.17	6.2
HBsIIR5	3	3	45	360	23.73	0.58	2.4	0.41	1.7	0.60	2.5	0.05	0.2	0.03	0.1	0.93	3.9
HBsIIR6	3	3	45	360	47.10	0.96	2.0	0.85	1.8	1.12	2.4	0.40	0.9	0.12	0.3	1.75	3.7
HBsIIR7	3	3	45	360	243.07	4.89	2.0	4.39	1.8	6.42	2.6	5.92	2.4	1.30	0.5	11.01	4.5
HBsIIR8	3	3	45	360	799.20	15.00	1.9	13.75	1.7	20.04	2.5	12.18	1.5	13.07	1.6	33.69	4.2

Seroconversion Study
Ten commercially available seroconversion panels were divided among the three ADVIA Centaur testing sites and were tested with the ADVIA Centaur HBsAgII assay. Reference testing was done using an FDA approved HBsAg assay for comparison. Testing at all sites was performed in singlicate and no additional repeat or confirmatory testing was done with these samples because of their limited volumes and well characterized nature.

The average difference in bleed days between ADVIA Centaur and the reference assay is +2.5 days. The performance of the ADVIA Centaur HBsAgII assay on these seroconversion panels is better or equal to that of the reference assay.

Seroconversion Summary Table

	HBsAg Positive Result from Initial Draw Date		Reference vs. ADVIA Centaur
Panel ID	Reference Assay (Days)	ADVIA Centaur Assay (Days)	Difference in Bleed Days[a]
11002	9	7	+2 (1 bleed)
11007	36	36	0
11008	79	69	+10 (2 bleeds)
11011	110	103	+7 (2 bleeds)
11012	18	18	0
11016	27	27	0
11017	42	40	+2 (1 bleed)
6280	13	13	0
6283	29	29	0
PHM925	8	4	+4 (1 bleed)

[a] The difference in bleed days is relative to the reference assay. For example a +2 means that the ADVIA Centaur HBsAgII assay detected HBsAg in a sample corresponding to 2 days before the reference assay detected HBsAg.

Prospective Population
The total prospective study population for the ADVIA Centaur HBsAgII testing consisted of 2119 patients. Of the 2119 patients collected prospectively, 1044 patients (49.3%) were from the high risk population, 818 patients (38.6%) were from the signs and symptoms population, 83 patients (3.9%) were from the dialysis population, 20 (0.9%) patients were transplant recipients, 86 were pregnant female (4.1%) and 68 were pediatric samples (3.2%). The study population was 19.9% Caucasian, 58.6% Black, 18.5% Hispanic, 1.8% Asian, 0.4 % American Indian/Alaskan native, and 0.8% other. The majority of the patients were male (61.8% male, 38.2% female).
Testing at the three study sites consisted of a single replicate on the ADVIA Centaur HBsAgII assay with repeat testing done on all initial reactives and confirmatory testing

for all repeat reactives in order to confirm the current testing algorithm. Reference testing was done for all of the above samples on an FDA approved HBsAg assay using a single initial replicate with additional repeat and confirmatory testing performed as recommended by the package insert.

The HBV disease classification for each patient was determined from the results obtained from serological assessment using hepatitis marker profiles determined using FDA-approved ADVIA Centaur reference assays (aHBs, HBsAg, aHBcM and HBcT). The HBV classification was based on the Reactive (+), Nonreactive (-), and Equivocal results of these four reference markers. There were 14 unique reference marker patterns observed. These patterns are listed below.

Classification by HBV Reference Markers

	HBsAg	aHBcM	HBcT	aHBs	Classification
1	+	-	-	-	Early Acute
2	+	+	+	-	Acute
3	+	+	+	+	Late Acute
4	+	-	+	+	Chronic
5	+	-	+	-	Chronic
6	+	-	-	+	Chronic
7	-	+	+	+	Early recovery
8	-	(Eqv)	+	+	Early recovery
9	-	+	+	-	Early recovery
10	-	+	-	+	Early recovery
11	-	-	-	+	Immune due to Hepatitis vaccination
12	-	-	+	+	Immune natural infection
13	-	-	+	-	Recovered
14	-	-	-	-	Not previously infected

+ = Reactive
- = Nonreactive
Eqv = Equivocal

The prospective population was evaluated by HBV classification and by percent agreement calculated between the ADVIA Centaur HBsAgII assay method and the reference assay for each specimen classification, including exact 95% (Clopper-Pearson) confidence intervals. Data is summarized in the following tables (Pediatric and Prenatal populations are analyzed separately).

Comparison of Results by HBV Classification (All Testing Sites)

Siemens ADVIA Centaur HBsAgII Assay Method Comparison in the Prospective General Study Population by HBV Classification ADVIA Centaur HBsAgII Assay vs. Reference HBsAg Assay All Testing Sites					
	Reference HBsAg Assay Nonreactive ADVIA Centaur HBsAgII Assay		Reference HBsAg Assay Reactive ADVIA Centaur HBsAgII Assay		
HBV Classification	**Nonreactive N**	**Reactive N**	**Nonreactive N**	**Reactive N**	**Total N**
Early Acute	0	0	0	4	**4**
Acute	0	0	0	10	**10**
Late Acute	0	0	0	2	**2**
Chronic	0	0	0	116	**116**
Early Recovery	22	0	0	0	**22**
Recovered	214	2	3	3	**222**
Immune due to natural infection	531	1	1	1	**534**
Immune due to hepatitis B vaccination	331	0	0	1	**332**
Not previously infected	722	0	1	0	**723**
Total	**1820**	**3**	**5**	**137**	**1965**

The corresponding negative and positive agreements are summarized in the table below.

Percent Agreement by HBV Classification (All Testing Sites)

Siemens ADVIA Centaur HBsAgII Assay Method Comparison in the General Study Population by HBV Classification ADVIA Centaur HBsAgII Assay vs. Rreference HBsAg Assay All Testing Sites				
HBV Classification	**Negative Agreement**		**Positive Agreement**	
	% (x/n)[a]	**95% CI**	**% (x/n)[b]**	**95% CI**
Early Acute	--- (0/0)	---	100.0 (4/4)	39.8 to 100.0
Acute	--- (0/0)	---	100.0 (10/10)	69.2 to 100.0
Late Acute	--- (0/0)	---	100.0 (2/2)	15.8 to 100.0
Chronic	--- (0/0)	---	100.0 (116/116)	96.9 to 100.0
Early Recovery	100.0 (22/22)	84.6 to 100.0	--- (0/0)	---
Recovered	99.1 (214/216)	96.7 to 99.9	50.0 (3/6)	11.8 to 88.2
Immune due to natural infection	99.8 (531/532)	99.0 to 100.0	50.0 (1/2)	1.3 to 98.7
Immune due to hepatitis B vaccination	100.0 (331/331)	98.9 to 100.0	100.0 (1/1)	2.5 to 100.0
Not previously infected	100.0 (722/722)	99.5 to 100.0	0.0 (0/1)	0.0 to 97.5
Total	**99.8 (1820/1823)**	**99.5 to 100.0**	**96.5 (137/142)**	**92.0 to 98.8**

a x = the number of ADVIA Centaur results that are nonreactive in agreement with reference assay

n = the number of nonreactive reference HBsAg results

b x = the number of ADVIA Centaur results that are reactive in agreement with reference assay

n = the number of reactive reference HbsAg results

Acute & Chronic Population Studies

A total of 156 acute and chronic samples were tested, including 24 acute samples that were acquired retrospectively. The samples were divided among the three sites. The acute and chronic specimens were tested as the other prospective populations with an

initial single replicate on the ADVIA Centaur HBsAgII assay with additional testing for initial reactives and confirmatory testing for all repeat reactives. Reference testing was done for all of the above samples on an FDA approved HBsAg assay using a single initial replicate with additional repeat and confirmatory testing done as recommended by the package insert.

Comparison of Results in the Acute and Chronic Population (All Testing Sites)

	Reference HBsAg Assay Nonreactive		Reference HBsAg Assay Reactive		
	ADVIA Centaur HBsAgII Assay		ADVIA Centaur HBsAgII Assay		
	Nonreactive	Reactive	Nonreactive	Reactive	Total
HBV Status	**N**	**N**	**N**	**N**	**N**
Acute	0	0	0	40	40
Chronic	0	0	0	116	116
All	*0*	*0*	*0*	*156*	*156*

Percent Agreement in the Acute and Chronic Population (By Site)

Testing Site	HBV Status	Negative Agreement % (x/n)[a]	95% CI	Positive Agreement % (x/n)[b]	95% CI
Site 1	Acute	--- (0/0)	---	100.0 (26/26)	86.8 to 100.0
	Chronic	--- (0/0)	---	100.0 (22/22)	84.6 to 100.0
	All	--- (0/0)	---	100.0 (48/48)	92.6 to 100.0
Site 2	Acute	--- (0/0)	---	100.0 (8/8)	63.1 to 100.0
	Chronic	--- (0/0)	---	100.0 (45/45)	92.1 to 100.0
	All	--- (0/0)	---	100.0 (53/53)	93.3 to 100.0
Site 3	Acute	--- (0/0)	---	100.0 (6/6)	54.1 to 100.0
	Chronic	--- (0/0)	---	100.0 (49/49)	92.7 to 100.0
	All	--- (0/0)	---	100.0 (55/55)	93.5 to 100.0
All Sites	Acute	--- (0/0)	---	100.0 (40/40)	91.2 to 100.0
	Chronic	--- (0/0)	---	100.0 (116/116)	96.9 to 100.0
	All	--- (0/0)	---	100.0 (156/156)	97.7 to 100.0

[a] x = the number of ADVIA Centaur results that are nonreactive in agreement with reference assay
n = the number of nonreactive reference assay results

[b] x = the number of ADVIA Centaur results that are reactive in agreement with reference assay
n = the number of reactive reference assay results

Pediatric Population Study

A total of 162 pediatric specimens that include both prospective as well as commercially purchased retrospective samples were divided among the three testing sites. In an additional study, nine HBsAg positive pediatric samples were retrospectively collected and tested. The pediatric population including both

nonreactive and reactive samples was tested as the other prospective populations with an initial single replicate on the ADVIA Centaur HBsAgII assay with additional testing for initial reactives and confirmatory testing for all repeat reactives. Reference testing was done for all of the above samples on an FDA approved HBsAg assay using a single initial replicate with additional repeat and confirmatory testing done as recommended by the assay package insert.

Comparison of Results in the Pediatric Population (All Testing Sites)

	Reference HBsAg Assay Nonreactive ADVIA Centaur HBsAgII assay		**Reference HBsAg Assay Reactive ADVIA Centaur HBsAgII assay**		
	Nonreactive	**Reactive**	**Nonreactive**	**Reactive**	**Total**
Age	**N**	**N**	**N**	**N**	**N**
5 to 22 months	7	0	0	0	7
2 to 12 years	58	0	0	0	58
13 to 21 years	95	0	0	2	97
All	160	0	0	2	162

Percent Agreement in the Pediatric Population (All Testing Sites)

	Negative Agreement		**Positive Agreement**	
Age	**% (x/n)[a]**	**95% CI**	**% (x/n)[b]**	**95% CI**
5 to 22 months	100.0 (7/7)	59.0 to 100.0	--- (0/0)	---
2 to 12 years	100.0 (58/58)	93.8 to 100.0	--- (0/0)	---
13 to 21 years	100.0 (95/95)	96.2 to 100.0	100.0 (2/2)	15.8 to 100.0
All	100.0 (160/160)	97.7 to 100.0	100.0 (2/2)	15.8 to 100.0

[a] x = the number of ADVIA Centaur results that are nonreactive in agreement with the reference assay
n = the number of nonreactive reference assay results
[b] x = the number of ADVIA Centaur results that are reactive in agreement with the reference assay
n = the number of reactive reference assay results

Nine additional HBsAg positive pediatric samples were retrospectively collected and tested.

	Reference HBsAg Assay Nonreactive ADVIA Centaur HBsAgII assay		**Reference HBsAg Assay HBsAg Reactive ADVIA Centaur HBsAgII assay**		
	Nonreactive	**Reactive**	**Nonreactive**	**Reactive**	**Total**
Age	**N**	**N**	**N**	**N**	**N**
5 to 22 months	0	0	0	0	0
2 to 12 years	0	0	0	1	1
13 to 21 years	3	0	0	5	8
All	3	0	0	6	9

Comparison of Results in the Total Pediatric Population

	Reference HBsAg Assay Nonreactive ADVIA Centaur HBsAgII assay		Reference HBsAg Assay Reactive ADVIA Centaur HBsAgII assay		
	Nonreactive N	Reactive N	Nonreactive N	Reactive N	Total N
5 to 22 months	7	0	0	0	7
2 to 12 years	58	0	0	1	59
13 to 21 years	98	0	0	7	105
All	163	0	0	8	171

Neonate Population Study

Twenty neonate serum (cord blood) samples were tested in single replicates with the ADVIA Centaur HBsAgII assay at Siemens Healthcare Diagnostics in Tarrytown, NY. Five additional neonatal or cord blood samples were retrospectively collected and spiked with HBsAg positive human serum to target the low positive end of the assay. The samples were split between two lots of ADVIA Centaur HBsAgII assay with each specimen being tested with one reagent lot. Reference testing was done using an FDA approved HBsAg assay with a neonatal claim, using a single initial replicate with additional repeat and confirmatory testing done as recommend by the package insert.

Twenty cord blood samples were retrospectively collected and tested in Tarrytown. All were nonreactive on both ADVIA Centaur and reference assay. The results are summarized in the following tables:

Comparison of Results in the Neonatal Population

Siemens ADVIA Centaur HBsAgII Assay Method Comparison In the Neonate (Cord Blood) Study Population ADVIA Centaur HBsAgII Assay vs. Reference HbsAg Assay				
Reference HBsAg Assay Nonreactive ADVIA Centaur HBsAgII Assay		Reference HBsAg Assay Reactive ADVIA Centaur HBsAgII Assay		Total
Nonreactive	Reactive	Nonreactive	Reactive	N
20	0	0	0	20

Percent Agreement in the Neonatal Population

Siemens ADVIA Centaur HBsAgII Assay Method Comparison In the Neonate (Cord Blood) Study Population ADVIA Centaur HBsAgII Assay vs. Reference HbsAg Assay			
Negative Agreement		Positive Agreement	
% (x/n)[a]	95% CI	% (x/n)[b]	95% CI
20	0	0	0

[a] x = the number of ADVIA Centaur results that are nonreactive in agreement with the reference assay
n = the number of nonreactive reference assay results

[b] x = the number of ADVIA Centaur results that are reactive in agreement with the reference assay
n = the number of reactive reference assay results

A total of 5 additional neonatal or cord blood samples were retrospectively collected and diluted with human serum to target the low positive end of the assay.

ADVIA Centaur HBsAgII assay vs. Reference HBsAg Assay				
Reference HBsAg Assay Nonreactive		**Reference HBsAg Assay Reactive**		
ADVIA Centaur HBsAgII assay		**ADVIA Centaur HBsAgII assay**		
Nonreactive	**Reactive**	**Nonreactive**	**Reactive**	**Total**
N	**N**	**N**	**N**	**N**
0	2	0	3	5

Pregnant Population Study

Prospectively and retrospectively collected samples from 320 pregnant women across all three trimesters were tested. The samples were divided among the three study sites. Approximately one third of the samples were tested with each lot; one lot per sample, with all three reagent lots used at each site. Samples from an additional 23 pregnant women were retrospectively collected and spiked with HBsAg positive serum to target the low positive end of the end of the assay. The analysis was stratified by trimester. The total pregnant population includes 86 prospectively collected and 257 retrospectively collected samples.

The specimens from pregnant women were tested as the other prospective populations with an initial single replicate with the ADVIA Centaur HBsAgII assay with additional testing for initial reactives and confirmatory testing for all repeat reactives. Reference testing was done for all samples on an FDA approved HBsAg assay using a single initial replicate with additional repeat and confirmatory testing performed as recommended by the assay package insert.

Comparison of Results in the Pregnant Population (All Testing Sites)

Trimester	Abbott Architect HBsAg Nonreactive / ADVIA Centaur HBsAgII Assay Nonreactive N	Abbott Architect HBsAg Nonreactive / ADVIA Centaur HBsAgII Assay Reactive N	Abbott Architect HBsAg Reactive / ADVIA Centaur HBsAgII Assay Nonreactive N	Abbott Architect HBsAg Reactive / ADVIA Centaur HBsAgII Assay Reactive N	Total N
1	91	0	1	1	93
2	109	0	0	0	109
3	118	0	0	0	118
All	318	0	1	1	320

Percent Agreement in the Pregnant Population (All Testing Sites)

Trimester	Negative Agreement % (x/n)[a]	Negative Agreement 95% CI	Positive Agreement % (x/n)[b]	Positive Agreement 95% CI
1	100.0 (91/91)	96.0 to 100.0	50.0 (1/2)	1.3 to 98.7
2	100.0 (109/109)	96.7 to 100.0	--- (0/0)	---
3	100.0 (118/118)	96.9 to 100.0	--- (0/0)	---
All	100.0 (318/318)	98.8 to 100.0	50.0 (1/2)	1.3 to 98.7

[a] x = the number of ADVIA Centaur® results that are nonreactive in agreement with Abbott Architect

n = the number of nonreactive Abbott Architect results

[b] x = the number of ADVIA Centaur® results that are reactive in agreement with Abbott Architect

n = the number of reactive Abbott Architect results

Samples from an additional 23 pregnant women were retrospectively collected and diluted with human serum to target the low positive end of the end of the assay. The analysis was stratified by trimester.

Trimester	Reference HBsAg Assay HBsAg Nonreactive / ADVIA Centaur HBsAgII assay Nonreactive N	Reference HBsAg Assay HBsAg Nonreactive / ADVIA Centaur HBsAgII assay Reactive N	Reference HBsAg Assay HBsAg Reactive / ADVIA Centaur HBsAgII assay Nonreactive N	Reference HBsAg Assay HBsAg Reactive / ADVIA Centaur HBsAgII assay Reactive N	Total N
1	0	4	0	6	10
2	0	2	0	4	6
3	0	2	0	5	7
All	0	8	0	15	23

Safety and Effectiveness Results of the Clinical Studies

Multi-centered clinical studies were conducted in the US. The observed clinical sensitivity and specificity of the ADVIA Centaur HBsAgII assay was comparable to current commercially available, FDA approved assays. The HBV classification of the prospective population showed 14 unique reference marker patterns. The reactive percent agreement between the ADVIA Centaur HBsAgII method and the reference assay was 96.5% with a 95% confidence interval (92.0% to 98.8%) and the nonreactive percent agreement was 99.8% with a 95% confidence interval (99.5% to 100.0%). Both the reactive and the nonreactive percent agreement results met the acceptance criteria of ≥90.0% and ≥99.0% respectively, between the ADVIA Centaur HBsAgII and the reference assay results when evaluated across all sites.

Acute and chronic HBs samples were evaluated with the ADVIA Centaur HBsAgII assay and compared to the reference assay to support the clinical utility of this assay with these particular populations. For both the acute and chronic populations there was 100.0% reactive agreement. There were no nonreactive samples. The acceptance criteria of reactive percent agreement ≥ 90% was met for both disease classifications at each site individually and for the test sites combined.

Pediatric samples were prospectively and retrospectively collected and tested with the ADVIA Centaur HBsAgII assay and a reference method. The reactive and nonreactive percent agreements between the ADVIA Centaur HBsAgII method and the reference assay were 100.0% (n=162). There were only 2 reactive samples within the original pediatric cohort. Nine additional HBsAg-positive pediatric samples were retrospectively collected and tested. Among these 9 samples, 6 tested reactive by both methods and 3 tested nonreactive by both methods.

To asses assay performance with neonatal samples 20 cord blood samples were retrospectively collected and tested with the ADVIA Centaur HBsAgII assay and a reference method. All 20 samples tested nonreactive by both assays. An additional 5 neonatal or cord blood samples were retrospectively collected and spiked with HBsAg-positive human serum to target the low-positive end of the assay. Among these 5 samples 3 tested reactive by both methods and 2 tested nonreactive by the Centaur HBsAgII assay and reactive by the reference assay.

A total of 320 samples from pregnant women were tested with the ADVIA Centaur HBsAgII assay and a reference assay. There was 100% negative agreement among samples in the original cohort and only two reactive pregnancy samples (one was reactive with both assays, the other was reactive by the reference assay and nonreactive with the ADVIA Centaur HBsAgII assay). Samples from an additional 23 pregnant women were retrospectively collected and spiked with HBsAg-positive human serum to target the low-positive end of the end of the assay. Within this cohort there were 15 samples that tested reactive by both methods and 8 samples that tested non-reactive by the reference method and reactive with the ADVIA Centaur HBsAgII assay.

Additional assessment of assay sensitivity was studied by testing a series of well-defined seroconversion panels with the Centaur HBsAgII assay and a reference assay and comparing the bleed date at which seroconversion occurred. In all cases the ADVIA Centaur HBsAgII assay detected seroconversion at least at the same bleed date as compared to the reference assay and in 5 out of 10 panels examined the HBsAgII assay detected seroconversion earlier than the reference assay. The average difference in bleed days was +2.5 days.

Precision and reproducibility of the Centaur HBsAgII assay was acceptable from run to run, day to day, reagent lot to reagent lot and site to site. Across all panel ranges with Index Value >2.0 and across all lots and sites, the %CV ranged from 1.9%-4.6% for the within-run estimates and from 4.2%-7.4% for the total precision estimates. The results met the acceptance criteria that, for those panel members with concentrations in the range 2.0 - 50.0 Index Value, all within-run %CV precision estimates are ≤15.0 % and the total %CV precision estimates are ≤20.0%.

Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included six investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the FDA Microbiology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM NONCLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

As an *in-vitro* diagnostic test the ADVIA Centaur HBsAgII and ADVIA Centaur HBsAg Confirmatory assays involve removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood is drawn.

False positive and false negative results are discussed in Section VIII. There were no adverse effects of the device reported while the study was conducted.

B. **Effectiveness Conclusions**

- The ADVIA Centaur HBsAgII and ADVIA Centaur HBsAg Confirmatory assays demonstrated acceptable analytical sensitivity as determined by limit of detection studies utilizing the WHO International Standard and through seroconversion studies.
- The results of the ADVIA Centaur HBsAgII within-laboratory precision and multi-site reproducibility studies demonstrated acceptable variability around the assay cut-off and across the assay range.
- The assay demonstrated the analytical ability to detect a panel comprised of the most common HBsAg mutants reported in the literature. The panel was composed of 24 recombinant mutant HBsAg samples and one native positive patient sample.
- The analytical specificity studies showed that there are no concerns with endogenous interferents at physiological levels, or with potential cross reactive agents.
- The assays demonstrated equivalent performance with serum and plasma samples.
- Sample stability with the ADVIA Centaur HBsAgII assay was demonstrated for up to 14 days (2-8°C) and can withstand 4 freeze/thaw cycles.
- The claimed reagent stability information was adequately substantiated by analytical study results. The real-time stability information provided supports a shelf life of 12 months when stored at 2-8°C.
- The clinical performance was evaluated in an ethnically diverse population representative of the intended use population and representative of the different HBV classification groups. The positive and negative percent agreement values for both the ADVIA Centaur HBsAgII and the ADVIA Centaur HBsAg Confirmatory assays were acceptable.

C. **Benefit-Risk Conclusions**

As a diagnostic test, the ADVIA Centaur HBsAgII 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 benefits to HBV-infected individuals tested by these assays outweigh 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.

In conclusion, given the available information above, the data support that for the qualitative detection of hepatitis B surface antigen (HBsAg) in human adult, adolescent, and pediatric serum and plasma, and neonatal samples using the

ADVIA Centaur or ADVIA Centaur XP systems the probable benefits outweigh the probable risks.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the instructions for use. The submitted clinical studies have shown that the ADVIA Centaur HBsAgII and the ADVIA Centaur HBsAg Confirmatory assays, when compared to reference clinical laboratory procedures, has a similar ability to detect the presence of HBsAg in human adult and pediatric serum and plasma (EDTA, lithium-heparin, or sodium-heparin), and neonatal samples. The rates of false positivity and false negativity are within acceptable limits compared to the reference assay. It has been shown that the device has no demonstrable cross-reactivity with the majority of viruses or organisms that may cause clinical hepatitis. Therefore, this device should benefit the physician in the diagnosis and management of HBV.

XIII. CDRH DECISION

CDRH issued an approval order on June 6, 2013

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.