SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:

Total antibodies to hepatitis B surface antigen
Total antibodies to hepatitis B surface antigen control material

Device Trade Names:

ADVIA Centaur Anti-HBs2 (aHBs2) Assay
ADVIA Centaur Anti-HBs2 (aHBs2) Quality Control Material for use on the ADVIA Centaur and ADVIA Centaur XP Systems

Applicant's Name and Address:

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

Date of Panel Recommendation:

None

Premarket Approval Application (PMA) Number:

P100039

Date of FDA Notice of Approval:

January 20, 2012

Expedited:

Not Applicable

II. INDICATIONS FOR USE

The ADVIA Centaur anti-HBs2 assay is an *in vitro* diagnostic immunoassay for the qualitative and quantitative determination of total antibodies to hepatitis B surface antigen in human adult, adolescent, and pediatric serum or plasma (EDTA, lithium-heparinized, or sodium-heparinized) and neonatal samples using the ADVIA Centaur and ADVIA Centaur XP systems. The assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection in individuals prior to or following HBV vaccination or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

This assay has not been FDA-cleared or approved for the screening of blood or plasma donors.

ADVIA Centaur aHBs2 Quality Control Material

For *in vitro* diagnostic use in monitoring the performance of the Anti-HBs2 assay on the ADVIA Centaur Systems. The performance of the Anti-HBs2 quality control material has not been established with any other anti-HBs assays.

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions for the ADVIA Centaur Anti-HBs2 (aHBs2) Assay and ADVIA Centaur Anti-HBs2 (aHBs2) Quality Control Material are stated in the respective product labeling.

V. DEVICE DESCRIPTION

The ADVIA Centaur Anti-HBs2 assay is a sandwich immunoassay using direct, chemiluminometric technology. HBsAg (ad and ay) is coupled to magnetic latex particles in the Solid Phase. In the Lite Reagent, the HBsAg (ad and ay) is labeled with acridinium ester. Non-magnetic latex particles are added from the ancillary well. The sample is incubated simultaneously with Lite Reagent, Solid Phase, and Ancillary Reagent. Antibody-antigen complexes will form if anti-HBs is present in the sample. The ADVIA Centaur system automatically performs the following actions:

- dispenses 100 µL of sample into a cuvette
- dispenses 50 µL of Lite Reagent and 20 µL of Ancillary reagent and incubates for 2.75 minutes at 37°C
- dispenses 125 µL of Solid Phase and incubates the mixture for 5.5 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 anti-HBs activity present in the patient sample and the amount of relative light units (RLUs) detected by the system.

ADVIA Centaur aHBs2 Quality Control Material:

Use of the ADVIA Centaur aHBs2 Quality Control Material is recommended for quality control. The controls, negative and positive, are used for monitoring the performance of the ADVIA Centaur Anti-HBs2 assay. The ADVIA Centaur aHBs2 Quality Control Material is a serum matrix and may not adequately control the assay for plasma specimens. The user should provide alternate control material for plasma.

Kit Configuration and Components

Reagents:

The ADVIA Centaur Anti-HBs2 assay is composed of the following reagents.

- ADVIA Centaur Anti-HBs2 ReadyPack:
  - Lite Reagent – inactivated human hepatitis B surface antigen (ad and ay) labeled with acridinium ester in protein buffer
  - Solid Phase – recombinant hepatitis B surface antigen (ad and ay) coupled to magnetic latex particles in protein buffer
  - Ancillary Reagent – non-magnetic latex particles in tris buffer with surfactant

- Wash 1 – phosphate buffer saline with sodium azide (<0.1%) and surfactant
- Multi-Diluent 11 – tris buffer with goat serum with protein stabilizers and preservatives
- Anti-HBs2 Calibrator Vials – processed human plasma positive for antibodies to HBsAg.

ADVIA Centaur aHBs2 Quality Control Material:

The ADVIA Centaur aHBs2 Quality Control Material kit consists of 2 vials of negative control and 2 vials of positive control manufactured from human plasma negative and positive for antibodies to HBsAg with preservatives.

Calibration

The ADVIA Centaur Anti-HBs2 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 into the system. The 2 calibrators in the kit are run when the lot is first used or after expiration of the calibrator interval. 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 assay utilizes a cutoff of 10 mIU/mL, which is equivalent to the anti-Hepatitis B Immunoglobulin 1st Reference Preparation. Individuals whose samples read at or above this level are considered to be immune from infection with HBV.

Interpretation of Results

The system reports anti-HBs antibody results in mIU/mL, and as reactive (positive), nonreactive (negative), or needing retest.

- Nonreactive: Samples with an initial value < 8 mIU/mL. Anti-HBs is below 10 mIU/mL and the patient is considered not to have protective immunity to HBV infection.
- Reactive: Samples with an initial value ≥ 12 mIU/mL. Anti-HBs is detected at ≥ 10 mIU/mL and the patient is considered to have protective immunity to HBV infection.
- Retest Zone: Samples with an initial value ≥ 8 and < 12 mIU/mL. If results are within the retest zone after initial testing, samples must be retested in duplicate. After retesting, if 3 results are available and 2 results are ≥ 10, then the sample is considered to be reactive. If 3 results are available and 2 results are < 10, then the sample is considered to be nonreactive.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection of Hepatitis B. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

There are currently several FDA approved *in vitro* diagnostic tests for measuring antibodies to hepatitis B surface antigen, which when used in conjunction with a patient's medical history, clinical examination, and other findings can be used for diagnostic purposes.

VII. MARKETING HISTORY

The ADVIA Centaur anti-HBs2 Assay is currently being marketed internationally in the following countries:

Australia
Singapore
Korea
Hong Kong
Canada
Austria
Belgium
Bulgaria
Croatia
Czech Republic
Cyprus
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Iceland
Ireland
Israel
Italy
Latvia
Liechtenstein
Lithuania
Luxembourg
Malta
New Zealand
Netherlands
Norway
Poland
Portugal
Romania
Serbia
Slovakia
Slovenia
South Africa
Spain
Sweden
Switzerland
Turkey
UK

This product has not been withdrawn from any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

When used according to the instructions in the package insert, there are no known potential 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.

A false nonreactive result would not necessarily be considered a public health risk, as the individual would either unnecessarily be vaccinated, or would be considered to have not recovered from an acute HBV infection.

A false reactive result could be considered a public health risk due to the fact that an individual would be considered to have been previously vaccinated, or had been previously exposed, and would be therefore immune to HBV. The risk is that an individual would not be vaccinated and would be at a higher risk of infection if exposed to HBV.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Limit of Blank and Limit of Detection

The Limit of Blank (LoB) for the ADVIA Centaur Anti-HBs2 assay was determined as recommended in CLSI guideline EP17-A. An anti-HBs negative base pool was used as a blank and was analyzed in 10 sample tubes on two different instruments over ten days. Each sample was tested using three different reagent lots with two replicate determinations daily. The LoB was calculated in accordance with CLSI guideline EP17-A and was determined to be 0.35 mIU/mL for the ADVIA Centaur Anti-HBs2 assay.

The Limit of Detection (LoD) was determined in accordance with CLSI guideline EP17-A. Five sample pools, prepared by spiking anti-HBs positive serum into anti-aHBs negative serum, had values ranging from 1.0 to 2.4 mIU/mL. The serum panel was analyzed with three different reagent lots on two instruments over 10 days. The mean, median and 5^{th} percentiles were calculated for each sample by reagent lot and by system. The LoD was calculated in accordance with CLSI guideline EP17-A and was determined to be 1.9 mIU/mL for this assay. However, the manufacturer will claim an LoD of 3.1 mIU/mL in the product labeling.

B. Standardization to WHO

The ADVIA Centaur Anti-HBs2 assay is standardized to the against the World Health Organization (WHO) 1st International Reference Preparation (1977). The WHO standard was spiked into four anti-HBs negative matrices (sodium heparinized

plasma, lithium heparinized plasma, EDTA plasma and serum) to target an anti-HBs dose of ~1000mIU/mL. The four spiked samples were then diluted with the corresponding base matrix at 2X, 4X, 8X, 16X, 32X, 64X and 128X to create 4 sets of pools with target anti-HBs concentrations spanning the assay range (up to 1000 mIU/mL). The ADVIA Centaur aHBs2 dose recovery of each diluted pool was calculated using 2 point calibration. The WHO dose recovery of the pools was calculated from a standard curve prepared with the WHO material. The mean ADVIA Centaur aHBs2 dose recovery was plotted against the mean WHO dose recovery. The results of the study showed that the ADVIA Centaur aHBs2 assay correlates well with the WHO Standard in all sample matrices.

C. **Linearity**

The WHO 1st IRP was spiked into four anti-HBs negative matrices (sodium heparinized plasma, lithium heparinized plasma, EDTA plasma and serum) to target an anti-HBs dose of ~1000 mIU/mL. The four spiked samples were then diluted with the corresponding negative serum matrix at 2X, 4X, 8X, 16X, 32X, 64X and 128X to create 4 sets of pools with target anti-HBs concentrations spanning the assay range (up to 1000 mIU/mL). The mean ADVIA Centaur aHBs2 observed dose recovery was plotted against the expected value. Linear regression analyses were done with all 3 replicates for each pool level. The results met the acceptance criteria where R is ≥ 0.95 in all matrices tested. The ADVIA Centaur Anti-HBs2 assay is linear up to 1000 mIU/mL anti-HBs.

Additionally, four separate high titer pools in different sample matrices were prepared with an anti-HBs concentration level of approximately 1000 mIU/mL. The doses of the high titer and low titer pools of each matrix were determined and the high and low pools were mixed at various ratios to create pools with intermediate levels of anti-HBs. The procedure was done for each sample matrix including serum and plasma (EDTA, lithium heparin, and sodium heparin). A total of 11 panel members (including the high and low pools) for each matrix were used and each panel member was tested in 4 replicates using the ADVIA Centaur aHBs2 assay. The mean observed aHBs recovery was plotted versus the expected recovery (values based on the dilution). The correlation coefficients (R) for each dilution series for the Patient Pools/Panels met the acceptance criteria of $R \geq 0.95$. The Anti-HBs2 assay is linear up to 1000 mIU/mL anti-HBs.

D. **Endogenous Interference**

The ADVIA Centaur Anti-HBs2 assay was tested following the guidelines described by the Clinical and Laboratory Standards Institute (CLSI) EP7-A2 for interference due to high levels of endogenous substances. The following levels of the following endogenous substances have been evaluated for their effect on the ADVIA Centaur anti-HBs2 assay recovery of spiked patient samples.

Serum specimens that are . . .	Demonstrate ≤ 15% 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 (high)	12 g/dL of total protein
proteinemic (low)	3 g/dL of total protein*
hyper IgG	6 g/dL of immunoglobulin G
biotin	500 ng/mL of biotin

* Demonstrates ≤ 15% change in results with protein as low as 3g/dL.

No clinically significant interference was observed in the performance of the ADVIA Centaur Anti-HBs2 assay up to the levels stated above.

E. Matrix Effects

Samples from 77 normal healthy donors were drawn into 4 different specimen collection tube types (serum, EDTA, lithium heparin, and sodium heparin) to evaluate any sample matrix effects. Blood tubes were centrifuged at 3000rpm (12000 x G), and the serum or plasma was decanted off. The samples were run with the ADVIA Centaur aHBs2 assay over multiple runs with multiple lots of reagents, calibrators, and controls.

The linear regression analyses of each plasma type vs. serum showed good correlation across the assay range between the anti-HBs values of serum and the different plasma samples collected in the different tube types.

Of the 77 samples tested in this matrix study, 11 samples were near the cut-off of 10 mIU/mL for Anti-HBs (ranging from 2.5 to 25 mIU/mL). Using these samples, the bias of the different plasma types to serum were calculated. Plasma samples collected with the EDTA showed a 10% positive bias, samples from sodium heparin tubes showed a 10% negative bias to serum whereas the lithium heparinzed plasma had an approximately 14% negative bias to serum.

F. High Dose Hook Effect

To assess any potential hook effect, two high activity anti-HBs samples were serially diluted using a negative anti-HBs basepool and then assayed in triplicate with 2 ADVIA Centaur Anti-HBs2 assay reagent lots. The results of this study showed samples with anti-HBs values up to 200,000 mIU/mL do not report results less than 1000 mIU/mL.

G. Stability Studies

1. Sample Stability

On-the-clot Specimen Storage:
A study was done to determine if storing the processed serum or plasma sample in the original collection tube ("On the Clot") rather than transferring the sample to secondary container affected the ADVIA Centaur Anti-HBs2 result.

Fresh samples from in-house normal healthy donors were drawn into the following tube types: sodium heparin plasma, lithium heparin plasma, EDTA

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plasma and serum. Primary tubes were centrifuged at 3000 rpm for 10 minutes at the zero time point. The centrifuged samples stored in primary tubes at 2 – 8°C were then tested with the ADVIA Centaur aHBs2 assay at the time points of 0 hour, 8 hours, 1 day, 2 days, 3 days and 7 days.

The clinical interpretation of the sample was the same regardless of time of centrifugation or tube type. There was no significant change to anti-HBs value compared to the baseline due to time to centrifugation or tube type up to 24 hours. Based on this study, samples can be stored in the primary collection tube for up to 7 days at 2 - 8°C.

Specimen Handling Studies:
The specimen handling studies were a series of experiments in which specimens collected in the sample matrices claimed as suitable for use in the ADVIA Centaur Anti-HBs2 method were subjected to potential stresses and then tested using the ADVIA Centaur Anti-HBs2 assay. Primary tubes were centrifuged at 3000 rpm at the zero time point for 10 minutes. The specimens were then aliquoted and stored at 2-8°C, room temperature (25°C), and -20°C. The stored aliquots were then evaluated at various test time points. All percentage recoveries were calculated against the baseline (day 0) value.

Additionally, samples stored frozen (-20°C) were subjected to 4 freeze-thaw cycles. Recoveries were compared to the samples that were not subjected to the freeze-thaw cycles.

Results from these sample handling studies showed that there were no changes in clinical interpretation or significant changes in anti-HBs values, and support the claims that samples can be subjected to the following:

1. Serum and EDTA plasma samples can be stored at room temperature for up to 7 days and heparinized plasma samples can be stored at room temperature up to 3 days.
2. Samples can be stored refrigerated (2-8°C) for up to 7 days.
3. Samples can be stored frozen (–20°C) for longer term storage (up to 45 days tested).
4. Samples can be frozen and thawed up to 4 times.

2. ADVIA Centaur Anti-HBs2 Reagent Stability

i. Reagent Real-Time Stability

Real-time stability studies were carried out using five lots of ADVIA Centaur Anti-HBs2 Readypack reagents, calibrators, and controls. All kits and reagents were stored at the recommended storage temperature of 2 to 8°C. Reagents and calibrators were evaluated at several checkpoints post manufacturing date.

The real time stability studies currently support a claim of 24 months of stability at 2-8°C for the ADVIA Centaur Anti-HBs2 reagents, calibrators, and controls.

ii. Reagent Onboard Stability

Four lots of Centaur Anti-HBs2 reagents have undergone reagent OBS studies on the ADVIA Centaur systems. Onboard stability testing occurred at several checkpoints after the reagents were placed onboard. Control recovery met the acceptance criteria for performance.

The on-board studies for the reagents support 90 days OBS and a 42-day recalibration for the ADVIA Centaur Anti-HBs2 reagents.

iii. Reagent shipping Stability

Shipping studies for the ADVIA Centaur Anti-HBs2 assay reagents indicated that the product tolerated 3 freeze/thaw/ cycles (-40°C to 2-8°C). Data from testing reagents stored at an elevated temperature (37°C) for 13 weeks were also used to assess shipping stability.

The recommended shipping conditions are to ship the ADVIA Centaur Anti-HBs2 reagents stored at 2 to 8°C.

3. ADVIA Centaur Anti-HBs2 Calibrator and Control Stability Studies

No open vial stability studies were performed on the ADVIA Centaur Anti-HBs2 Calibrators and Controls. The Calibrators and Controls are the same products used in the FDA approved ADVIA Centaur Anti-HBs assay; the only difference is the Calibrators and Controls are value assigned for the ADVIA Centaur Anti-HBs2 assay.

4. Instrument Studies

Environmental Testing

The purpose of environmental testing is to assess ADVIA Centaur Anti-HBs2 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 then calculated.

The studies demonstrated acceptable performance of the ADVIA Centaur Anti-HBs2 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 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, in rare occasions, a Wash Pack with a solution other than water may be required.

The ADVIA Centaur anti-HBs2 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 anti-HBs2 assay. Results of this study determined that no mitigations were necessary.

H. Antimicrobial Effectiveness Testing

The ADVIA Centaur Anti-HBs2 reagents contain 0.25% Micr-O-protect as the preservative 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. The test involved seven microorganisms. Results indicated that the preservative systems for reagents met the USP requirements for antimicrobial effectiveness testing.

Calibrators and QC Controls were not tested since they are the same products used in the FDA approved ADVIA Centaur Anti-HBs assay; the only difference is the Calibrators and Controls are value assigned for the ADVIA Centaur Anti-HBs2 assay.

I. Precision

Precision measurements were conducted to evaluate repeatability, and the intermediate precision of within laboratory precision according to CLSI guideline EP5-A2.

Internal precision

Precision was performed following the guidelines of CLSI EP5-A2. The study was run using two lots of ADVIA Centaur Anti-HBs2 reagent (with respective calibrators) on one ADVIA Centaur system for 20 days with 2 runs per day. The work list consisted of calibrators (lot specific), controls, and an eight (8) member sample panel in 4 different matrices (Serum, EDTA, Sodium Heparin, and Lithium Heparin). The anti-HBs concentrations in the sample panels ranged from ~ 3.5 to 865 mIU/mL. A calibration run was performed at the start of the study and a second calibration was performed on Day 10 of the study. The matrix reproducibility results from a representative lot of reagent are presented in the following table:

Sample	# Date	# Run	# Cuv	MEAN (mIU/mL)	Within Run SD	Within Run CV	Total SD	Total CV
EDTA E2	20	40	80	3.90	0.24	6.1	0.32	8.1
EDTA E3	20	40	80	9.22	0.27	2.9	0.46	5.0
EDTA E4	20	40	80	14.25	0.40	2.8	0.71	4.9
EDTA E5	20	40	80	96.37	1.95	2.0	4.14	4.3

Sample	# Date	# Run	# Cuv	MEAN (mIU/mL)	Within Run SD	Within Run CV	Total SD	Total CV
EDTA E6	20	40	80	242.19	4.89	2.0	9.76	4.0
EDTA E7	20	40	80	498.94	9.51	1.9	18.16	3.6
EDTA E8	20	40	80	585.71	12.39	2.1	24.59	4.2
EDTA E9	20	40	80	790.82	16.88	2.1	32.45	4.1
Li-Hep H2	20	40	80	4.76	0.22	4.7	0.36	7.5
Li-Hep H3	20	40	80	10.64	0.29	2.7	0.60	5.7
Li-Hep H4	20	40	80	17.40	0.35	2.0	0.78	4.5
Li-Hep H5	20	40	80	176.53	3.78	2.1	7.56	4.3
Li-Hep H6	20	40	80	309.24	5.86	1.9	12.70	4.1
Li-Hep H7	20	40	80	513.01	10.59	2.1	20.19	3.9
Li-Hep H8	20	40	80	599.40	13.67	2.3	34.79	5.8
Li-Hep H9	20	40	80	850.42	15.61	1.8	36.36	4.3
Na-Hep N2	20	40	80	3.87	0.21	5.4	0.33	8.6
Na-Hep N3	20	40	80	8.75	0.24	2.7	1.01	11.5
Na-Hep N4	20	40	80	15.05	0.31	2.0	0.69	4.6
Na-Hep N5	20	40	80	55.80	1.33	2.4	2.56	4.6
Na-Hep N6	20	40	80	206.53	3.82	1.9	8.21	4.0
Na-Hep N7	20	40	80	362.26	8.01	2.2	13.67	3.8
Na-Hep N8	20	40	80	617.49	13.19	2.1	23.06	3.7
Na-Hep N9	20	40	80	863.73	16.88	2.0	29.21	3.4
SER R1	20	40	80	3.07	0.16	5.1	0.28	9.2
SER R2	20	40	80	6.17	0.23	3.7	0.43	6.9
SER R3	20	40	80	12.73	0.30	2.3	0.66	5.2
SER R4	20	40	80	19.99	0.54	2.7	1.00	5.0
SER R5	20	40	80	128.29	3.16	2.5	6.21	4.8
SER R6	20	40	80	382.66	7.07	1.8	14.79	3.9
SER R7	20	40	80	606.61	14.86	2.4	23.68	3.9
SER R8	20	40	80	870.12	17.37	2.0	34.38	4.0

External Precision

Precision was further evaluated incorporating between-run, between-day, between-lot and between-site variation. The ADVIA Centaur Anti-HBs2 reproducibility study was performed at 2 external sites and an internal site utilizing 2 reagent lots per site. An 8-member serum panel was assayed in replicates of 4 in 2 runs per day over at least 5 days for each lot. The study was completed with a single calibration of the assay (one calibration interval).

The data from all 3 sites and from all 3 reagent lots were combined to obtain SD and percent CV for within run, between run, between testing site, between lot, and total. The precision estimates were derived from variance component analysis. The reproducibility results are presented in the following table:

Panel Member	Mean Concentration (mIU/mL)[1]	Within Run[2]		Between Run[3]		Between Testing Site[4]		Between Lot[5]		Total[6]		Number of Observations
		SD[7]	CV (%)	SD[7]	CV (%)	SD[7]	CV (%)	SD[7]	CV (%)	SD[7]	CV (%)	
1	3.1	0.22	7.0	0.11	3.4	0.37	12.0	0.20	6.6	0.49	16.1	248
2	6.3	0.27	4.4	0.17	2.7	0.49	7.8	0.25	4.0	0.64	10.2	248
3	13.1	0.39	2.9	0.31	2.4	0.73	5.6	0.37	2.8	0.96	7.3	248
4	20.7	0.56	2.7	0.43	2.1	1.05	5.1	0.58	2.8	1.39	6.7	248
5	133.7	2.86	2.1	2.60	1.9	5.45	4.1	4.23	3.2	7.91	5.9	248
6	401.8	8.14	2.0	7.51	1.9	14.16	3.5	13.77	3.4	22.65	5.6	248
7	638.7	15.01	2.4	15.86	2.5	23.34	3.7	24.46	3.8	40.33	6.3	248
8	906.8	17.65	1.9	16.10	1.8	31.56	3.5	23.04	2.5	45.80	5.1	234
Positive Control	115.9	2.72	2.4	3.29	2.8	6.03	5.2	1.45	1.2	7.53	6.5	164

1 Arithmetic mean of all results (all testing sites and reagent lots)

2 Variability of the assay performance within day (all testing sites and reagent lots)

3 Variability of the assay performance between days (all testing sites and reagent lots)

4 Variability of the assay performance between testing sites (from testing site to testing site)

5 Variability of the assay performance between reagent lots (from reagent lot to reagent lot, across all testing sites)

6 Variability of the assay performance incorporating all testing sites, all reagent lots, and all days

7 SD of mean concentration (mIU/mL)

J. Analytical Specificity

The ADVIA Centaur Anti-HBs2 assay was evaluated for potential cross reactivity with viral antibodies and disease state specimens. The nonreactive anti-HBs status of each specimen was verified using a commercially available reference anti-HBs assay. The following results were obtained on the ADVIA Centaur Anti-HBs2 assay:

Clinical Category	*# aHBs Ref Nonreactive*	*# aHBs2 Nonreactive*	*# aHBs2 Reactive*
Hepatitis A Infection (HAV)	17	17	0
Hepatitis B Infection (HBsAg +)	12	12	0
Hepatitis C Infection (HCV)	24	24	0
Non-viral Liver Disease	8	8	0
Rheumatoid Arthritis	8	8	0
Autoimmune Disease (Systemic Lupus & ANA)	15	15	0
Influenza Vaccination	6	6	0
Syphilis Infection	9	9	0
Cytomegalovirus (CMV)	13	13	0
Herpes Simplex Virus I/II (HSV)	22	22	0
Toxoplasma gondii Infection	12	12	0
Human Immunodeficiency Virus (HIV)	9	9	0

Clinical Category	# aHBs Ref Nonreactive	# aHBs2 Nonreactive	# aHBs2 Reactive
Rubella IgG	34	34	0
Varicella-Zoster Virus (VZV)	31	31	0
Epstein-Barr Virus (EBV)	54	54	0
Total	**274**	**274**	**0**

K. Seroconversion Analysis

The ADVIA Centaur aHBs2 assay was evaluated with five commercially available HBV seroconversion panels and compared to an FDA approved Anti-HBs Reference method. The results demonstrated that the first reactive time point (bleed date) for the ADVIA Centaur Anti-HBs2 occurred at the same time as the Reference method for all panels tested.

The comparison of the seroconversion detection between the assays in terms of days (where applicable) is summarized in the table below:

Panel ID	Days to change in reactivity of Anti-HBs results				Difference in Days to ADVIA Centaur Anti-HBs2 Reactivity (Reference-anti-HBs2)
	Reference Anti-HBs		ADVIA Centaur Anti-HBs2		
	NR[a]	RX[b]	NR	RX	
6281	43	50	43	50	0
6509	70	84	70	84	0
935B	118	134	118	134	0
950[c]		Bleed #2 of 4		Bleed #2 of 4	N/A
PHM[c]		Bleed #2 of 4		Bleed #2 of 4	N/A

a) NR = non-reactive
b) RX = reactive
c) bleed dates not provided

X. SUMMARY OF PRIMARY CLINICAL STUDY

The safety and effectiveness of the ADVIA Centaur Anti-HBs2 assay was determined by a clinical trial consisting of the following studies:

The population study is comprised of a total of 2030 prospectively collected samples including; 1098 samples from individuals who were at high risk for HBV infection due to lifestyle, behavior, occupation, or known exposure events; 828 samples from individuals who had signs or symptoms of HBV infection; 83 samples from individuals who were undergoing dialysis; and 21 samples from individuals who had received an organ transplant. These samples were tested using FDA approved HBV assays and their HBV status classified on the basis of the HBV marker results. These samples were tested with both the ADVIA Centaur® Anti-HBs2 assay and a reference Anti-HBs assay at the clinical trial sites.

A total of 110 pediatric specimens, including nonreactive and reactive samples, and purchased from a commercial source, were tested with the ADVIA Centaur aHBs2 assay and a reference Anti-HBs assay at the clinical trial sites.

Twenty neonate serum (cord blood) samples that were purchased commercially were tested. Each sample was split into aliquots; one aliquot was tested with the ADVIA Centaur aHBs2 assay at one clinical trial and another aliquot was tested with a reference anti-HBs assay at a clinical laboratory as part of routine testing.

Twenty–seven matched Pre- and post-HBV vaccine samples that were purchased commercially were tested with the ADVIA Centaur aHBs2 assay and a reference Anti-HBs assay at the clinical trial sites.

The prospective study population for the ADVIA Centaur Anti-HBs2 assay consisted of 2030 patients. Of these 2030 patients, 1098 patients (54.09%) were from the high risk population, 828 patients (40.79%) were from the signs and symptoms population, 83 patients (4.09%) were from the dialysis population, and 21 patients (1.03%) were transplant recipients. The prospective study population was 60.15% Black, 19.80% Caucasian, 17.04% Hispanic, 1.77% Asian, 0.39% American Indian or Alaskan Native, and 0.84% from unknown or other ethnicity. The majority of patients were male (64.43% male and 35.57% female). The mean age was 46.0 years (range of 13 to 91 years). Patients in the prospective study population were from the following geographic regions: Florida (55.67%), District of Columbia (23.94%), Texas (11.18%), California (5.32%), Maryland (3.15%) and other states (0.74%). The ADVIA Centaur Anti-HBs2 results for the prospective population for all sites combined by age group and gender are summarized in the following table:

Distribution of High Risk, Signs and Symptoms, Dialysis, and Transplant Recipient Population by Age Group and Gender (All Testing Sites)

Age (Years)	Gender	Reactive (N)	Nonreactive (N)	Total (N)
0–9	Male	0	0	0
	Female	0	0	0
10–19	Male	8	4	12
	Female	8	3	11
20–29	Male	74	48	122
	Female	43	31	74
30–39	Male	61	105	166
	Female	35	59	94
40–49	Male	216	235	451
	Female	125	131	256
50–59	Male	216	232	448
	Female	88	130	218
60–69	Male	32	58	90
	Female	24	28	52
≥ 70	Male	4	15	19
	Female	4	13	17
All	Male	611	697	1308
	Female	327	395	722
Total		938	1092	2030

Prospective Study

The HBV disease classification for all patients in the high risk, signs and symptoms, transplant and dialysis populations (2030 patients total) was determined by serological assessment using resultant hepatitis marker profiles obtained from results of commercially available, FDA approved reference assays. The serological assessment included the following 4 HBV markers: hepatitis B virus surface antigen (HBsAg), total antibody to hepatitis B virus core antigen (anti-HBc Total), IgM antibody to hepatitis B core antigen (anti-HBc IgM), and total antibody to hepatitis B virus surface antigen (anti-HBs). Testing of these specimens occurred at each study site. The individual ADVIA Centaur HBV assay result was compared to the reference HBV assay result and to the patient classification.

The HBV disease classification for each patient considered to be high risk for HBV infection, presenting with signs and symptoms of HBV infection, undergoing dialysis treatment, or a transplant recipient (2030 total) in the prospective study was determined by serological assessment using resultant hepatitis marker profiles obtained from results of commercially available, FDA-approved reference assays. The serological assessment included the following 4 HBV markers: HBsAg, anti-HBc Total, and anti-HBc IgM, and anti-HBs. Testing of these specimens occurred at the 3 external study sites.

Each patient's HBV infection was classified based on the reactive (+)/nonreactive (–) patterns of the 4 HBV reference serological markers. Disease classification for each patient was based only on the HBV serological marker results, and was not affected by additional laboratory or clinical information. There were 14 unique reference marker patterns observed. These patterns are presented in the table below.

Classification by HBV Reference Markers (All Testing Sites)

	HBV Reference Markers			
HBV Classification	**HBsAg**	**IgM Anti-HBc**	**Total Anti-HBc**	**Anti-HBs**
Early Acute	+	-	-	-
Acute	+	+	+	-
Late Acute	+	+	+	+
Chronic	+	-	+	+
Chronic	+	-	+	-
Chronic	+	-	-	+
Early Recovery	-	+	+	+
Early Recovery	-	Equivocal	+	+
Early Recovery	-	+	+	-
Early Recovery	-	+	-	+
Immune due to hepatitis vaccination	-	-	-	+
Immune natural infection	-	-	+	+
Recovered	-	-	+	-
Not Previously Infected	-	-	-	-

+ = Reactive

– = Nonreactive

Following the assignment of specimen classification, the HBV results obtained using the ADVIA Centaur Anti-HBs2 assay were compared with results obtained using the reference anti-HBs assay for each result category (reactive and nonreactive). Specimens with an anti-HBs2 value and/or an anti-HBs value within the retest zone were retested and interpreted as described under *Interpretation of Results*.

The method comparison for all the prospectively collected samples (the high risk, signs and symptoms, dialysis and transplant populations) across all testing sites and by site is presented in the following table.

Comparison of Results in High Risk, Signs and Symptoms, Dialysis, and Transplant Recipient Populations by HBV Classification
ADVIA Centaur Anti-HBs2 Assay versus Reference Anti-HBs Assay (All Testing Sites)[1]

	Reference Anti-HBs Assay Nonreactive		Reference Anti-HBs Assay Reactive		
	ADVIA Centaur Anti-HBs2 Assay		ADVIA Centaur Anti-HBs2 Assay		
HBV Classification	Reactive (N)	Nonreactive (N)	Reactive (N)	Nonreactive (N)	Total (N)
Early Acute	0	8	0	0	8
Acute	0	10	0	0	10
Late Acute	0	0	0	2	2
Chronic	0	112	6	1	119
Early Recovery	0	2	20	0	22
Immune due to hepatitis vaccination	1	2	362	6	371
Immune due to natural infection	0	8	522	9	539
Recovered	13	207	3	2	225
Not Previously Infected	11	723	0	0	734
Total	**25**	**1072**	**913**	**20**	**2030**

1 In this study, 73 of 2030 specimens (3.6%) fell within the aHBs2 retest zone. Thirty-four of these specimens (46.6%) were determined to be reactive after retesting.

The percent agreements for the entire prospective study between the ADVIA Centaur Anti-HBs2 assay and the reference anti-HBs assay across all testing sites is summarized in the following table.

Percent Agreement and Confidence Intervals by HBV Classification in High Risk, Signs and Symptoms, Dialysis, and Transplant Recipient Populations
ADVIA Centaur Anti-HBs2 Assay versus Reference Anti-HBs Assay (All Testing Sites)

HBV Classification	Positive Percent Agreement % (x/n)	95% Exact Confidence Interval	Negative Percent Agreement % (x/n)	95% Exact Confidence Interval
Early Acute			100 (8/8)	68.8–100
Acute			100 (10/10)	74.1–100
Late Acute	0 (0/2)	0–77.6		
Chronic	85.7 (6/7)	42.1–99.6	100 (112/112)	97.4–100
Early Recovery	100 (20/20)	86.1–100	100 (2/2)	22.4–100
Immune due to Hepatitis B vaccination	98.4 (362/368)	96.5–99.4	66.7 (2/3)	9.4–99.2
Immune due to natural infection	98.3 (522/531)	96.8–99.2	100 (8/8)	68.8–100
Recovered	60 (3/5)	14.7–94.7	94.1 (207/220)	90.1–96.8
Not Previously Infected			98.5 (723/734)	97.3–99.3
Total	**97.9 (913/933)**	**96.7–98.7**	**97.7 (1072/1097)**	**96.7–98.5**

Adolescent / Pediatric Study

One hundred ten (110) retrospectively collected pediatric specimens were purchased commercially. The samples were obtained from subjects with ages ranging from 1-17. The nonreactive and reactive percent agreements between the assays were calculated and are presented in the table below:

		Reference anti-HBs Assay		
ADVIA Centaur Anti-HBs2 Assay		**Reactive**	**Nonreactive**	**Total**
	Reactive	59	2	61
	Nonreactive	3	46	49
	Total	62	48	110

% Overall Agreement = 95.5% (105/110)
95% Confidence Interval: 89.7% to 98.5%

% Reactive Agreement = 95.2% (59/62)
95% Confidence Interval: 86.5% to 99.0%

%Nonreactive Agreement = 95.8% (46/48)
95% Confidence Interval: 85.8% to 99.5%

Neonate Study

Twenty (20) retrospectively collected neonate serum (cord blood) samples were tested with the ADVIA Centaur aHBs2 assay at one clinical trial and another aliquot was tested with a reference anti-HBs assay that is FDA approved for use with neonate samples at a clinical laboratory as part of routine testing.

The nonreactive and reactive percent agreements are presented below.

		Reference Anti-HBs Assay		
ADVIA Centaur anti-HBs2 Assay		**Reactive**	**Nonreactive**	**Total**
	Reactive	9	0	9
	Nonreactive	0	11	11
	Total	9	11	20

% Overall Agreement = 100.0% (20/20)
95% Confidence Interval: 86.1% to 100.0%

% Reactive Agreement = 100.0% (9/9)
95% Confidence Interval: 71.7% to 100.0%

%Nonreactive Agreement = 100.0% (11/11)
95% Confidence Interval: 76.2% to 100.0%

HBV Vaccinee Study (Pre- and Post-)

Twenty–seven matched Pre- and post-HBV vaccine samples that were purchased commercially were tested with the ADVIA Centaur aHBs2 assay and a reference Anti-HBs assay at the clinical trial sites.

Comparison of ADVIA Centaur Anti-HBs2 and Reference Anti-HBs Results in Pre- and Post-Vaccinated Populations[1]

	Reference Anti-HBs Results		
ADVIA Centaur Anti-HBs2 Results	Nonreactive (N)	Reactive (N)	Total (N)
Pre-vaccination			
Nonreactive, N (%)	26 (100%)	0	26 (100%)
Reactive, N (%)	0	0	0
Percent agreement: 100%			
95% confidence interval: 89.1–100			
Post-vaccination			
Nonreactive, N (%)	0	0	0
Reactive, N (%)	0	26 (100%)	26 (100%)
Percent agreement: 100%			
95% confidence interval: 89.1–100			

1 For the vaccinee panel (samples from 26 patients), the percent agreement between ADVIA Centaur Anti-HBs2 results and reference results was determined for pre-vaccination and for post-vaccination.

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 PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. Based on the results of the preclinical and clinical laboratory studies, the ADVIA Centaur Anti-HBs2 (aHBs2) Assay and ADVIA Centaur Anti-HBs2 (aHBs2) Quality Control Material, when used according to the provided directions and in conjunction with other serological and clinical information, should be safe and effective and pose minimal risk to the patient due to false test results.

B. Effectiveness Conclusions

The effectiveness of the ADVIA Centaur Anti-HBs2 has been demonstrated for use in determining if antibodies to the surface antigen of the hepatitis B virus are present in an individual's serum or plasma. A reasonable determination of effectiveness of the ADVIA Centaur Anti-HBs2 assay for aiding in the diagnosis of immunity and status of HBV infection in suspected individuals has been demonstrated.

C. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The submitted clinical studies have shown that the ADVIA Centaur anti-HBs2 assay, when compared to reference clinical laboratory procedures, has a similar ability to detect and quantitate antibodies to hepatitis B surface antigen in specimens from individuals at high risk for HBV infection, individuals with signs and symptoms of HBV infection, dialysis patients, organ transplant recipients, and HBV vaccine recipients. The rate 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 of HBV.

XIII. CDRH DECISION

CDRH issued an approval order on January 20, 2012.

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.