

## Summary of Safety and Effectiveness

### I. GENERAL INFORMATION

Device Generic Name: Hepatitis B Surface Antigen (HBsAg Assay)  
Hepatitis B Surface Antigen Confirmatory (HBsAg Conf assay)  
Hepatitis B Surface Antigen Positive and Negative Control materials

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

Applicant's Name and Address: Bayer HealthCare LLC  
511 Benedict Avenue  
Tarrytown, NY 10591-5097

Date(s) of Panel Recommendation: None.

Premarket Approval Application (PMA) Number: P030049

Date of Notice of Approval to Applicant: May 26, 2005

### II. INDICATIONS FOR USE

ADVIA Centaur® HBsAg Ready Pack Indications for use:

The ADVIA Centaur® HBsAg assay is an *in vitro* immunoassay for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum and plasma (potassium EDTA, lithium or sodium heparinized,) using the ADVIA Centaur® system. 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.

ADVIA Centaur® HBsAg Confirmatory Ready Pack Indications for use:

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

ADVIA Centaur® HBsAg Quality Control Material Indications for Use:

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For monitoring the performance of the HBsAg and HBsAg Confirmatory assays on the ADVIA Centaur® Systems.

### III. CONTRAINDICATIONS

None known

### IV. WARNINGS AND PRECAUTIONS

For in vitro diagnostic use only.

Warnings and precautions for ADVIA Centaur® HBsAg ReadyPack Reagents, the ADVIA Centaur® HBsAg ReadyPack Calibrators, ADVIA Centaur® HBsAg Confirmatory ReadyPack Reagents, and the ADVIA Centaur® HBsAg Quality Control Material are stated in the respective product labeling.

### V. DEVICE DESCRIPTION

#### Kit Configuration and Components

The ADVIA Centaur® HBsAg assay contains the following components:

<i>Reagent Pack</i>	<i>Reagent</i>	<i>Ingredients</i>
ADVIA Centaur® HBsAg ReadyPack primary reagent pack	Solid Phase	Streptavidin-coated magnetic latex particles in buffer with bovine serum albumin, goat serum, surfactant, sodium azide (<0.1%) and preservatives
ADVIA Centaur® HBsAg ReadyPack ancillary reagent pack	Lite Reagent	Biotinylated monoclonal mouse anti-HBsAg antibody reactive to the "a" region determinant (~1.0 µg/ mL) and acridinium ester-labeled monoclonal mouse anti-HBsAg antibody reactive to the "a" region determinant (~0.1 µg/mL) in buffer with bovine serum albumin, bovine gamma globulin, goat serum, mouse IgG, surfactant, sodium azide (< 0.1%) and preservatives
HBsAg calibrator vials	Calibrators	High calibrator: purified human HBsAg in buffer with sodium azide (<0.1%) low calibrator: processed normal human plasma with sodium azide (< 0.1%)

The ADVIA Centaur® HBsAg Confirmatory assay contains the following components:

- 1 ReadyPack primary reagent pack containing ADVIA Centaur® HBsAg Solid Phase and Ancillary Reagent
- ADVIA Centaur® HBsAg Master Curve card
- ADVIA Centaur® HBsAg Confirmatory Master Curve card
- 1 vial HBsAg Low Calibrator
- 1 vial HBsAg High Calibrator
- ADVIA Centaur® HBsAg Calibrator Assigned Value card

The ADVIA Centaur® HBsAg Controls contain the following components:

- 2 vials of Negative Control
- 2 vials of Positive Control
- Expected Values Card and barcode

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The following are required, but not furnished with the ADVIA Centaur® HBsAg Assay:

- ADVIA Centaur® Instrument
- ADVIA Centaur® Ancillary Probe Wash 1
- ADVIA Centaur® HBsAg quality control material
- ADVIA Centaur® Wash 1

All human source components have been tested with FDA approved methods for anti-HIV 1 and 2, anti-HCV, HBV surface antigen and found to nonreactive. The human source calibrators and positive control contains HBsAg and are treated with a BPL-UV inactivation procedure to render the material noninfectious.

### **Assay Principle and Procedure**

The ADVIA Centaur® HBsAg assay is a monoclonal antibody sandwich immunoassay using direct, chemiluminometric technology. Non-magnetic latex particles are added from the ancillary well. The Lite Reagent, packaged in a ReadyPack ancillary reagent pack, contains a biotinylated anti-HBs mouse monoclonal capture antibody and an acridinium-ester labeled anti-HBs mouse monoclonal antibody. HBsAg in the sample complexes with the antibodies and Streptavidin coated magnetic latex particles in the Solid Phase capture the HBsAg-antibody complexes.

The sample is incubated simultaneously with Solid Phase, Lite Reagent, and Ancillary Reagent. Antibody-antigen complexes will form if hepatitis B surface antigen is present in the sample.

Sample is first incubated with the Lite Reagent for 6 minutes at 37°C. During this incubation biotinylated anti-HBs monoclonal antibody and acridinium conjugated anti-HBs monoclonal antibody bind to HBsAg present in the sample. The Solid Phase and non-magnetic microparticles are added next, and the streptavidin-coated microparticles in the Solid Phase bind the biotin of the sample HBsAg / acridinium conjugated anti-HBs / biotinylated anti-HBs complex during an 18 minute incubation at 37°C. The microparticles are then held fast by a magnet and washed multiple times to remove unbound sample. The reaction mix is next reacted with acid and base to initiate a chemiluminescent reaction of the bound acridinium ester. The chemiluminescent signal is detected and quantified as relative light units (RLUs) by the photomultiplier tube (PMT) of the ADVIA Centaur® Instrument. The relative light units (RLUs) detected by the ADVIA Centaur® system are used to calculate the Index Value from the Master Curve. The RLU value is compared to a stored calibration curve to generate a patient result.

The ADVIA Centaur® HBsAg Confirmatory assay uses the principle of specific antibody neutralization to confirm the presence of HBsAg in a sample that is repeatedly reactive in the HBsAg assay. The sample is pretreated and tested in parallel; one sample aliquot is dispensed and incubated with a neutralizing reagent containing high titers of anti-HBs (Reagent A); the second sample aliquot is incubated with a non-neutralizing control reagent (Reagent B). HBsAg in the patient sample is bound by the anti-HBs in Reagent A and not allowed to react in the ADVIA Centaur® HBsAg assay. When both aliquots are run in the ADVIA Centaur® HBsAg assay, the inhibition of the RLU signal in the aliquot with Reagent A is compared to the RLU signal in the aliquot with Reagent B. The relative percent neutralization is calculated and an interpretation of the sample is generated. If the RLU value with Reagent B is below the cut off, the assay is invalid. If percent neutralization is >50% the sample is confirmed positive for HBsAg.

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### **Calibration**

The ADVIA Centaur® HBsAg assay utilizes a factory set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The master curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values on the system. The 2 calibrators in the kit are run when the lot is first used or after expiration of the calibration interval (21 days). 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 ADVIA Centaur® HBsAg Confirmatory assay utilizes the same calibrators as the HBsAg assay but has its own Master Curve card.

### **Assay antigen/antibody Description**

#### **HBsAg Assay**

The ADVIA Centaur® HBsAg assay utilizes biotinylated anti-HBs mouse monoclonal antibody (directed to the HBsAg “a” region determinant) and AE-labeled anti-HBs mouse monoclonal antibody in the Lite Reagent.

#### **HBsAg Confirmatory Assay**

The basis for the ADVIA Centaur® HBsAg Confirmatory assay is specific antibody neutralization prior to antibody/antigen interaction. An aliquot of the sample to be tested is pretreated with high titers of antibody to HBsAg (human anti-HBs; Reagent A) and then tested in the ADVIA Centaur® HBsAg assay. In parallel, an aliquot of the sample is pretreated by incubation with non-neutralizing control reagent (decalcified human plasma) that does not contain high titers of antibody to HBsAg (Reagent B). Hepatitis B virus surface antigen in the patient sample is bound by the anti-HBs in Reagent A and is not allowed to react in the ADVIA Centaur® HBsAg assay.

## **VI. ALTERNATIVE PRACTICES OR PROCEDURES**

Determination of the presence of HBsAg in patients may be achieved by using a number of commercially available, FDA licensed/approved, serological tests. When the results of such tests are evaluated in conjunction with a physician’s assessment and other biochemical test results, a diagnosis of infection with HBV can be established.

## **VII. MARKETING HISTORY**

The ADVIA Centaur® HBsAg and ADVIA Centaur® HBsAg Confirmatory Assays are currently being marketed internationally in accordance with section 802 of the Food Drug and Cosmetic act in the following countries: Colombia, Sweden, Norway, Finland, France, Germany, Italy, Spain, Portugal, United Kingdom, Belgium, Austria, South Africa, Japan, China, Hong Kong, Singapore, Malaysia, Korea, Australia, and New Zealand. This product has not been withdrawn from any country for any reason.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The ADVIA Centaur® HBsAg ReadyPack Reagents, ADVIA Centaur® HBsAg Confirmatory Reagents, and ADVIA Centaur® HBsAg Calibrators are for in vitro diagnostic use, thus there is no direct adverse effect on the patient.

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Failure of the product to perform as intended, or errors in the use of the product, may lead to a false result.

### **ADVIA Centaur® HBsAg Assay**

A false reactive (false positive) result with an HBsAg assay is not usually considered a patient or public health concern. A reactive result in the clinical lab setting is usually accompanied with results for additional HBV or biochemical markers or followed up with supplemental testing such as neutralization. In screening of pregnant women, there is a potential consequence to the newborn of receiving unnecessary therapy. If the mother tests positive for HBsAg, it is recommended that the newborn be given hepatitis B immune globulin (HBIG) and HBV vaccine within 12 hours of birth. A false positive result would therefore expose the newborn to the risk of receiving human source material.

A false non-reactive (false negative) result with an HBsAg assay is a concern primarily in screening of pregnant women. A false negative test would mean that a newborn may not receive treatment and would be at higher risk of acute or chronic HBV infection.

No HBsAg assay can guarantee to detect all infectious individuals. An individual may have antigen levels too low to be detected or the antigen produced may not be detectable due to genetic mutation. Because of the complexity of the mutations that can occur, no manufacturer can guarantee to detect all infectious donors and patients.

### **ADVIA Centaur® HBsAg Confirmatory Assay**

A false “confirmed” result when using an HBsAg Confirmatory assay is not considered a patient or public health concern because the results in both the neutralized sample and the non-neutralized control would have to be incorrect to report a false confirmation. If this did occur the implications would be the same as for the HBsAg test.

A false negative (not confirmed) result when using a HBsAg Confirmatory assay could occur due to a falsely increased signal in the neutralized sample, perhaps due to sample integrity or other malfunction, which would give the appearance that the sample had not neutralized. Were this to occur, the implication would be the same as for the HBsAg assay.

## IX. SUMMARY OF PRECLINICAL STUDIES

### **Laboratory Studies**

The objectives of the laboratory studies were to test the analytical sensitivity, dynamic range, potential cross-reactive specimens, endogenous interferences, high dose hook effects, precision, matrix/collection and tube type effects, sample handling, stability, microbial studies, and instrument studies for performance characteristics of the ADVIA Centaur® HBsAg and ADVIA Centaur® HBsAg Confirmatory assays.

### **Analytical Sensitivity**

The sensitivity of the ADVIA Centaur® HBsAg assay was evaluated using the WHO 1<sup>st</sup> International Reference Standard, low titer performance panels, and *ad* subtype and *ay* subtype HBsAg Sensitivity Panels.

Dilutions of the WHO 1<sup>st</sup> International Reference Standard 80/549-1 were tested with multiple reagent lots. A concentration of 0.1 IU/mL was consistently positive with all lots while a concentration of 0.05 IU/mL was always negative. By regression analysis the HBsAg concentration at the cut off (Index =1.0) was 0.066 IU/mL (95% CL = 0.0658 – 0.0662). Four commercially available low titer panels were used to assess the sensitivity of the assay for

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known positive samples in the assay cut off range. The panels were tested with multiple reagent lots and the ADVIA Centaur® HBsAg assay was reactive on 100% of the positive panel members.

The *ad* and *ay* subtype sensitivity panels were evaluated with multiple reagent lots. For the *ad* subtype sensitivity panel, HBsAg concentrations greater than or equal to 0.05 Paul Ehrlich Institute (PEI) Units/mL were detected 100% of the time. HBsAg concentrations of less than or equal to 0.03 PEI Units/mL were detected 0% of the time. The HBsAg concentration at the assay's assigned cut-off (1.0 Index) was estimated from the linear regression analysis as 0.034 PEI Units/mL (95% CL = 0.028 - 0.040).

For the *ay* subtype sensitivity panel, HBsAg concentrations greater than or equal to 0.03 Paul Ehrlich Institute Units/mL were detected 100% of the time. HBsAg concentrations of less than or equal to 0.02 PEI Units/mL were detected 0% of the time. The HBsAg concentration at the assay's cut-off (1.0 Index) was estimated from the linear regression analysis as 0.033 PEI Units/mL (95% CL 0.032 - 0.034).

The following table summarizes these testing results:

Series	Cutoff (Index = 1.0)	95% Exact Confidence Interval
WHO 1 <sup>st</sup> IRP Standard, 80/549	0.066 IU/mL	0.0658 – 0.0662
Commercially available HBsAg Sensitivity panel ( <i>ad</i> subtype)	0.034 PEI Units/mL	0.028 – 0.04
Commercially available HBsAg Sensitivity panel ( <i>ay</i> subtype)	0.033 PEI Units/mL	0.032 – 0.034

The ADVIA Centaur® HBsAg assay was tested with an HBV genotype panel to demonstrate performance against HBV genotypes A-F. All 17 panel members were detected by the assay.

To demonstrate confirmation of low positive samples by the ADVIA Centaur® HBsAg Confirmatory assay, 11 commercially available seroconversion panels and one low titer panel were tested. Of the 62 seroconversion panel samples that were reactive on the ADVIA Centaur® HBsAg assay, 59 were confirmed positive; the other 3 being “invalid” (control reagent was below the cut off, these specimens were not repeated). All the detected positive samples on the low titer panel were confirmed positive on ADVIA Centaur® HBsAg Confirmatory assay.

The above information demonstrates the ability of the ADVIA Centaur® HBsAg to be analytically sensitive for the detection of HBsAg.

### **Potential Cross-Reactive Specimens**

The specificity of the ADVIA Centaur® HBsAg assay was evaluated by testing 205 distinct serum specimens from 22 potentially cross-reacting groups. Patient samples from the following groups were tested: HAV antibody, HCV antibody, VZV, CMV, EBV, HSV-1, Syphilis, Toxoplasma IgM, Toxoplasma IgG, Rubella, Non-viral Liver Disease, Human anti-mouse antibodies (HAMA), Systemic Lupus Erythematosus, Rheumatoid factor, and Anti-nuclear antibody (ANA) specimens. Of these 22 sub-groups, 202 out of 205 specimens were observed to be non-reactive. One ANA specimen and 2 anti-HIV positive specimens were reactive. The following table shows testing result summary:

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<b>HBsAg Cross Reactor Summary Table</b>			
Sample Group	Number Tested	Centaur® HBsAg assay non-reactive	Centaur® HBsAg assay reactive
Rheumatoid Factor	9	9	0
ANA – SLE	7	6	1*
Rubella IgG <sup>+</sup>	10	10	0
Non Viral Liver Disease	10	10	0
HAV total	5	5	0
HCV IgG <sup>+</sup>	10	10	0
VZV IgG <sup>+</sup>	10	10	0
CMV IgG <sup>+</sup>	10	10	0
HAMA	9	9	0
Flu vaccine recipient	10	10	0
Toxoplasma IgM	7	7	0
Toxoplasma IgG	8	8	0
EBV IgG <sup>+</sup>	10	10	0
EBV IgM <sup>+</sup>	10	10	0
Syphilis	10	10	0
HSV-1 IgG <sup>+</sup>	10	10	0
HSV-1 IgM <sup>+</sup>	10	10	0
HCV +	10	10	0
HIV +	10	8	2**
Rubella IgM+	10	10	0
CMV IgM+	10	10	0
VZV IgM+	10	10	0
<b>Total Samples</b>	<b>205</b>	<b>202</b>	<b>3</b>

\* One sample was repeatedly reactive and not confirmed with the ADVIA Centaur® HBsAg Confirmatory assay

\*\* Two Samples were repeatedly reactive and confirmed positive for HBsAg with the ADVIA Centaur® HBsAg Confirmatory assay

In order to determine whether organisms other than HBV would cross-react or interfere with the ADVIA Centaur® HBsAg assay the following organisms, at the concentrations listed, were spiked into HBsAg nonreactive and HBsAg reactive specimens.

<b>HBsAg results of various bacterial spikes</b>		
Spike Material	Reactivity before spike	Reactivity after spike
S. aureus 1,000 CFU/mL	Non-reactive	Non-reactive
S. aureus 10,000 CFU/mL	Non-reactive	Non-reactive
P. aeruginosa 1,000 CFU/mL	Non-reactive	Non-reactive
P. aeruginosa 10,000 CFU/mL	Non-reactive	Non-reactive
E. coli 1,000 CFU/mL	Non-reactive	Non-reactive
E. coli 10,000 CFU/mL	Non-reactive	Non-reactive
S. aureus 1,000 CFU/mL	Reactive	Reactive
S. aureus 10,000 CFU/mL	Reactive	Reactive
P. aeruginosa 1,000 CFU/mL	Reactive	Reactive
P. aeruginosa 10,000 CFU/mL	Reactive	Reactive
E. coli 1,000 CFU/mL	Reactive	Reactive
E. coli 10,000 CFU/mL	Reactive	Reactive

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HBsAg results of various viral antigen spikes		
Spike Material	Reactivity before spike	Reactivity after spike
Epstein-Barr Virus 1 µg/mL	Non-reactive	Non-reactive
Epstein-Barr Virus 1 ng/mL	Non-reactive	Non-reactive
Cytomegalovirus 1 µg/mL	Non-reactive	Non-reactive
Cytomegalovirus 1 ng/mL	Non-reactive	Non-reactive
Rubella 1 µg/mL	Non-reactive	Non-reactive
Rubella 1 ng/mL	Non-reactive	Non-reactive
Varicella Zoster Virus 1 µg/mL	Non-reactive	Non-reactive
Varicella Zoster Virus 1 ng/mL	Non-reactive	Non-reactive
Epstein-Barr Virus 1 µg/mL	Reactive	Reactive
Epstein-Barr Virus 1 ng/mL	Reactive	Reactive
Cytomegalovirus 1 µg/mL	Reactive	Reactive
Cytomegalovirus 1 ng/mL	Reactive	Reactive
Rubella 1 µg/mL	Reactive	Reactive
Rubella 1 ng/mL	Reactive	Reactive
Varicella-Zoster Virus 1 µg/mL	Reactive	Reactive
Varicella-Zoster Virus 1 ng/mL	Reactive	Reactive

The submitted information shows that the ADVIA Centaur® HBsAg assays should have minimal, if any, cross-reactivity with the specimens that contain the organisms at or below the concentrations tested. Several organisms that cause hepatitis disease were not tested, e.g., hepatitis A virus, parvovirus B19, and hepatitis E virus. Therefore, the user should be aware that it is unknown whether these organisms will cross-react or interfere with the ADVIA Centaur® HBsAg assays. It is believed that this issue is adequately covered by the labeling listing for the organisms tested.

### **Endogenous Interferents**

The potentially interfering effects of conjugated bilirubin, unconjugated bilirubin, hemoglobin, triglycerides, hyper IgG, and low protein were evaluated using 10 specimens following the guidelines described by CLSI EP7-P<sup>1</sup> for interference due to endogenous substances. The effects of conjugated bilirubin at 40 mg/dL, unconjugated bilirubin at 40 mg/dL, hemoglobin at 500 mg/dL, triglycerides at 1000 mg/dL, hyper IgG at 6 g/dL (i.e., high total protein), and low protein at 3 g/dL were evaluated in serum specimens. No interference was found.

### **High Index Hook Effect**

The Centaur® HBsAg assay was evaluated for decrease of Index value in specimens containing extremely high HBsAg levels by spiking purified HBsAg (*ad* and *ay* subtypes) into negative serum and preparation of a series of dilutions with each subtype. It was determined that the ADVIA Centaur® HBsAg reagents will not hook below the cut-off value (index < 1.0) at the HBsAg concentrations tested (approximately 5 mg/mL) for either the *ad* or *ay* subtypes.

### **Precision Studies**

A single instrument CLSI EP5-A<sup>2</sup> precision study was done at Bayer Diagnostics using one lot of ADVIA Centaur® HBsAg Reagents. The study was set up as both an evaluation of HBsAg assay imprecision and a study of the effect of sample matrix (serum vs. five plasma anti-

<sup>1</sup> CLSI, Interference testing in chemistry; Approved guideline. CLSI document EP7-A (ISBN 1-56238-480-5). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA 2002.

<sup>2</sup> CLSI, Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline. CLSI document EP5-A [ISBN 1-56238-368-X]. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 1999.)

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coagulants) on specimen precision. For each anti-coagulant, a single specimen was used to prepare a five member panel targeting the following HBsAg INDEX ranges (high HBsAg positive serum was used to prepare spiked positive panel members);

- 0.0 INDEX (negative, un-spiked)
- 0.5 INDEX (elevated negative, spiked)
- 2.0 INDEX (low positive #1, spiked)
- 4.0 INDEX (low positive #2, spiked)
- 20.0 INDEX (positive, spiked).

Each sample was run twice a day in triplicate for 20 days. A new set of sample aliquots was thawed and mixed/centrifuged for each day of the study. Index values of the positive control, and spiked HBsAg specimen panels prepared in serum and three plasma types were calculated using a stored curve established by 2-point calibrator adjustment of the reagent master curve. The within-run and total assay precision (%CVs) of all samples with an Index > 1.0 (cut-off value) ranged from 1.8% to 4.7% and from 2.5% to 5.6% respectively. The following table shows summary study information:

Sample	Mean Index	Within-run		Among run		Among Date		Total	
		SD	CV(%)	SD	CV(%)	SD	CV(%)	SD	CV(%)
Positive Control	4.76	0.09	1.9	0.09	1.8	0.09	2.0	0.16	3.3
Serum 1	0.56	0.04	7.2	0.01	2.5	0.03	5.5	0.05	9.4
Serum 2	1.82	0.06	3.2	0.05	2.5	0.04	2.1	0.08	4.6
Serum 3	3.57	0.07	2.0	0.04	1.2	0.06	1.7	0.10	2.9
Serum 4	17.07	0.37	2.2	0.34	2.0	0.39	2.3	0.64	3.7
K2 EDTA 1	0.49	0.05	9.8	0.04	7.4	0.02	3.7	0.06	12.8
K2 EDTA 2	1.86	0.07	3.6	0.00	0.0	0.05	2.6	0.08	4.5
K2 EDTA 3	3.93	0.11	2.7	0.03	0.9	0.09	2.2	0.14	3.6
K2 EDTA 4	19.13	0.37	2.0	0.36	1.9	0.26	1.4	0.58	3.1
Lithium heparin 1	0.36	0.04	9.7	0.02	6.6	0.03	7.0	0.05	13.7
Lithium heparin 2	1.77	0.08	4.6	0.04	2.1	0.04	2.5	0.10	5.6
Lithium heparin 3	3.77	0.08	2.1	0.06	1.6	0.06	1.6	0.11	3.0
Lithium heparin 4	16.92	0.30	1.8	0.20	1.2	0.24	1.4	0.43	2.5
Sodium heparin 1	0.42	0.50	11.2	0.02	3.8	0.02	5.4	0.05	13.0
Sodium heparin 2	2.08	0.10	4.7	0.04	1.8	0.00	0.0	0.10	5.0
Sodium heparin 3	3.72	0.10	2.8	0.07	1.9	0.00	0.0	0.13	3.4
Sodium heparin 4	19.87	0.39	2.0	0.43	2.2	0.20	1.0	0.62	3.1

### **Matrix, Collection Tube Type, Effects Collection Tube Type**

Blood was collected from 50 individuals into serum glass, serum plastic, K<sub>2</sub>EDTA plastic, lithium heparin glass, lithium heparin plastic, sodium heparin glass, sodium heparin plastic, serum separator tube (SST) glass, and SST plastic. All serum and plasma donors were initially screened to be HBsAg and anti-HBs negative. Specimens used for positive spikes were screened to be anti-HBs negative. Using a high titer HBsAg plasma pool, specimens were spiked to reach HBsAg target levels covering low cut-off positives (2 - 8 ADVIA Centaur® Index (Index)) and high positive samples (50 - 150 Index). The distribution of the samples included in the study was twenty negatives, eleven low cut-off positives, and nineteen high

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positives. For evaluation purposes, the positive specimens were grouped into five groups with the following serum glass index ranges for each group:

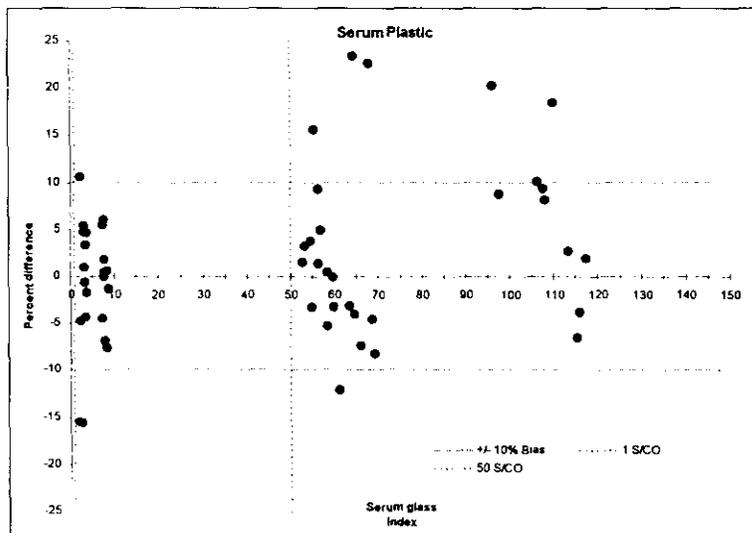
	n	Serum Glass Min <sup>1</sup> Index	Serum Glass Max <sup>2</sup> Index	Serum Glass Mean Index	Serum Plastic Min Index	Serum Plastic Max Index	Serum Plastic Mean Index	LiHeparin <sup>3</sup> Glass Min Index	LiHeparin Glass Max Index	LiHeparin Glass Mean Index
Group 1	12	2.1	3.6	2.9	2.1	3.7	2.9	1.7	3.2	2.6
Group 2	10	7.5	8.1	7.8	7.2	8.1	7.8	6.6	7.5	7.2
Group 3	20	53.6	68.9	59.9	53.9	81.5	60.9	50.8	64.9	57.3
Group 4	10	103.0	115.6	108.8	109.6	123.0	116.0	100.0	134.2	114.6
Group 5	8	125.2	143.5	136.3	119.5	132.4	127.2	104.1	126.8	113.6

1 = Minimum

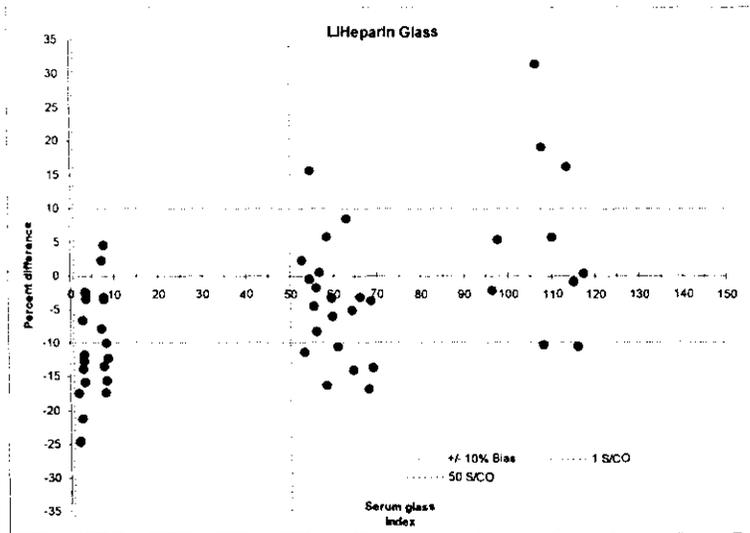
2 = Maximum

3 = Lithium Heparin

Results for the serum glass specimens were considered the reference results. Bias for the various specimen collection devices were determined by calculating the index percent difference from serum glass for each individual result. These results were then graphed with the x-axis showing serum index result and the y-axis showing percent difference from serum. The following two graphs show the results for serum plastic and sodium lithium glass.



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Based on the results obtained it was determined that the following blood collection tubes are acceptable for use in the ADVIA Centaur® HBsAg and HBsAg Confirmatory assays: serum plastic, K<sub>2</sub>EDTA plastic, serum separator tube (SST) glass, and SST plastic. For these anti-coagulants, the specimen index did not appreciably vary as a function of collection tube type. Due to the variation noted with lithium heparin glass, lithium heparin plastic, sodium heparin glass, and sodium heparin plastic it was determined that specimens collected with these devices that produced results  $\geq 0.7$  to 0.99 required additional testing, which may include other HBV serological marker and supplemental tests.

### Sample Handling Studies

The sample handling studies are a series of experiments in which specimens collected in all of the sample matrices claimed as suitable for use with the Centaur® HBsAg assay are subjected to potential stresses such as freeze/thaw or elevated temperature storage and tested in comparison to baseline data to determine the impact of the stress on assay accuracy. The sample handling studies described here evaluate the effect of the following patient sample handling conditions on ADVIA Centaur® HBsAg Index:

1. Extended time on-board the Centaur® Instrument (simulated by non-capped storage at 25°C).
2. Extended time in refrigerated (2-8°C) storage.
3. Extended time at room temperature (25°C) storage.
4. Extended time in freezer (-20°C) storage.
5. Multiple freeze/ thaw (-20°C/2-8°C) cycles.

Samples were collected during in-house blood draws from healthy donors in serum and plasma with a variety of anti-coagulants. The serum and plasma samples were aliquoted and placed in appropriate storage/stress conditions on the day of collection. A baseline Index value for each sample was established by testing with the ADVIA Centaur® HBsAg assay on the day of collection. All percent recoveries were calculated against this baseline (day 0) value. Results from the ADVIA Centaur® HBsAg sample handling studies support the claims that samples can

## Summary of Safety and Effectiveness

be subjected to the following conditions and still generate accurate results when tested in the ADVIA Centaur® HBsAg assay:

1. Samples can be kept on-board the Centaur® instrument for up to 8 hours.
2. Samples can be stored refrigerated (2-8°C) for up to 14 days.
3. Samples can be stored at room temperature for up to 8 hours.
4. Samples can be stored frozen (-20°C) for long term storage.
5. Samples can be frozen and thawed up to six times.

### **On-The-Cells Specimen Storage**

A study was done to determine if storing the processed serum or plasma sample in the original collection tube (“On the Cells”) rather than transferring the serum or plasma to a secondary container affects the ADVIA Centaur® HBsAg Index. Fresh samples were drawn from 10 healthy in-house donors into serum and plasma collection tube types. The specimens were centrifuged within the specified study times and an aliquot from each primary tube placed in another container (HBsAg positive specimens were spiked with high positive HBsAg pool before removing the aliquot). The samples were then stored at 2-8°C and tested side by side (on-the-cells versus plasma or serum) in the ADVIA Centaur® HBsAg assay at 1, and 3 days after collection. There is no evidence of any effect on the final assay result for the following specimen types: serum plastic, K<sub>2</sub>EDTA plastic, sodium heparin glass, sodium heparin plastic, serum separator tube (SST) glass, and SST plastic due to sample being left in the primary collection tube for up to three days of 2-8°C storage. The study show that specimens collected in lithium heparin (glass and plastic) may be left in the primary collection tube for up to 12 hours at 2-8°C.

### **Sample Processing – Time to Centrifugation**

A study was done to determine the effect of fresh sample time to centrifugation on the HBsAg Index. Ten (10) specimens were drawn from healthy in-house donors in serum collection tubes. The tubes were spiked with HBsAg positive pool and centrifuged shortly after collection and after 24 hours. Aliquots from the tubes were then tested on the ADVIA Centaur® to determine if leaving blood unprocessed in the collection tube for as long as 24 hours caused the specimen’s ADVIA Centaur® HBsAg index to shift. There was no apparent change in clinical results, i.e., reactive or nonreactive, when centrifugation was delayed up to 24 hrs.

### **Sample Handling – Inversion of Gel barrier Collection tubes**

A study was done to determine if inversion of barrier gel blood collection tubes interferes with ADVIA Centaur® HBsAg assay results. Blood was drawn from 22 healthy in-house donors using serum and plasma (Lithium Heparin) gel barrier (separator) collection tubes. Seven sample tubes were spiked with HBsAg at different levels, three were left negative and 12 specimens were spiked to levels close to the 1.0 Index cut-off. The tubes were rocked for 30 minutes, centrifuged, and an aliquot was taken. The tubes were then inverted 5 times and a second aliquot was taken. The two aliquots were compared to determine if inversion altered sample Index. Inversion of the barrier gel collection tube, 5 times, had no apparent effect on the assay results for both positive and negative samples.

### **Stability Studies**

## Summary of Safety and Effectiveness

Three lots of HBsAg reagents (Centaur® ReadyPack reagents, calibrators, and controls) were used for real time stability studies. All kits and reagents were stored at the recommended storage temperature of 2-8°C. Reagents and calibrators were monitored at several check points post manufacturing date. The submitted shelf-life studies support a claim of a 52 week expiration dating at 2-8°C for the HBsAg reagents. Three lots of the ADVIA Centaur® HBsAg Confirmatory Reagents were placed on real time stability studies. All kits and reagents were stored at the recommended storage temperature of 2-8°C. Reagents were monitored at several checkpoints post manufacturing date. The submitted shelf-life studies support a claim of a 104 week expiration dating at 2-8°C for the HBsAg Confirmatory Reagents.

To determine the shelf life for assay controls and calibrators, three lots of calibrators and three lots of controls have been placed on 2-8°C long-term stability. All calibrators and controls were stored at the recommended storage temperature of 2-8°C. Calibrators and controls were monitored at several checkpoints post manufacturing date. The submitted shelf-life studies support a claim of 12 month expiration dating at 2-8°C for the ADVIA Centaur® HBsAg calibrators and controls.

**Reagent On-Board Stability (OBS) and Calibration Interval Studies:** Two lots of reagents have undergone reagent OBS studies on two Centaur® instruments. OBS testing on the instruments occurred at several checkpoints after the reagents are placed on-board. A fresh pack serves as the control for each time-point. It was determined that a dose recovery within 10% or 2SD of the fresh pack serves to define acceptable performance. A calibration interval of 21 days was also evaluated using these results. The submitted on-board studies for the reagents support 41 days OBS (999 hours) for the ADVIA Centaur® HBsAg reagents. The OBS studies also support a re-calibration interval of 21 days.

To support reagent shipping recommendations shipping studies of the reagents found that the HBsAg reagents could withstand 3x freeze/thaw cycles (-40°C to 4°C) without aggregation of the solid phase and acceptable assay performance. The recommended shipping conditions are to ship the ReadyPack reagents in an upright position and stored at 2-8°C. A calibrator and control shipping study was performed on one manufactured lot. The HBsAg Calibrators and controls underwent 3x freeze/thaw cycles with no adverse effects.

The calibrator and control open vial study examined the length of time the calibrator or control is stable once the vial is opened. Open vials are stored at the recommended storage conditions of 2-8°C. The open vials are sampled periodically up to 90 days post initial opening. Fresh (unopened) vials are evaluated at each time point to serve as controls. The acceptance criterion for this study was dose recovery within 10% (or 2SD) of the fresh vial dose. The submitted study information supports an open vial use lifetime of up to 90 days.

### **Microbiology Studies**

The ADVIA Centaur® HBsAg and HBsAg Confirmatory reagents contain amphotericin, gentamicin, and sodium azide as preservatives to protect against contamination by microorganisms. The ADVIA Centaur® calibrators and Negative Control contain 0.09 % sodium azide and the Positive Control contains 0.25% Micro-O-Protect as preservatives to protect against contamination by microorganisms. The reagents and calibrators were challenged in a study conducted according to United States Pharmacopeia (USP) requirements for Antimicrobial Effectiveness testing to assess the ability of the reagents to withstand or control microbial contamination. Results indicated that the preservative systems for reagents and calibrators met the USP requirements for antimicrobial effectiveness testing.

A performance microbial challenge was performed using one lot of ADVIA Centaur® HBsAg and HBsAg Confirmatory reagents, calibrators, and controls. Reagents and controls were

## Summary of Safety and Effectiveness

inoculated with two pools of microbes containing the USP defined organisms at 10E3 and 10E6 CFU/mL and then run on the ADVIA Centaur® instrument at time 0 (Baseline), 30 days and 60 days. Controls, medical decision pools, and a quality control panel were all within expected ranges when tested using inoculated reagents at all timepoints.

### **Instrument Studies**

Software and hardware verification testing were performed for the *ADVIA Centaur*. Appropriate information and study results were furnished demonstrating that the *ADVIA Centaur*® hardware and software, used with the *ADVIA Centaur*® HBsAg reagents, functioned as described and had appropriate safeguards

### **Environmental Testing**

The purpose of environmental testing is to assess ADVIA Centaur® HBsAg and HBsAg Confirmatory assay control recovery or percent neutralization and interpretations at the mean and extreme environmental conditions as specified (18 to 30 °C). Each assay was calibrated and run on a single instrument unit in an environmental chamber. These studies demonstrated acceptable performance of the HBsAg and HBsAg Confirmatory assays when performed on instruments operating at the extremes of the temperature range for the ADVIA Centaur® instrument (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 scheduling options, using multiple water washes, or, in rare occasions where a Wash Pack with a solution other than water may be required.

The ADVIA Centaur® HBsAg assay and HBsAg Confirmatory assay were evaluated for their potential affect on all other assays using the same reagent probes and for the affect of all the other assay reagents on the HBsAg or HBsAg Confirmatory assay. To be accepted there must be < 5% difference in Index (or dose) between test and control, or no statistically significant change in Index (or dose), or no more than 1SD difference in Index (or dose) as appropriate for the assay and the control being tested. The submitted studies show that the HBsAg primary (ReadyPack) reagent has no compatibility issues with assays that share a common probe. It was demonstrated that the HBsAg ancillary reagent would interfere with some ADVIA Centaur® immunoassays. To correct this issue Ancillary Probe washes were instituted in the assay software to mitigate this interference. It was demonstrated that HBsAg Confirmatory Reagent A and Reagent B ancillary reagents have no compatibility issues with other assays.

### **Conclusions Drawn from the Pre-Clinical Studies**

The ADVIA Centaur® HBsAg assay was evaluated to demonstrate performance claims for cross-reactivity, interference, precision, matrix type, specimen handling, and reagent stability. The results of the pre-clinical studies demonstrated that the ADVIA Centaur® HBsAg reagents and instrument were capable of detecting HBsAg and with the assay there was minimal adverse effect on performance when other factors were included.

## X. SUMMARY OF CLINICAL STUDIES

The objective of this clinical study was to assess the efficacy of ADVIA Centaur® HBsAg for detecting hepatitis B surface antigen in human serum as presumptive evidence of an HBV infection.

## Summary of Safety and Effectiveness

### **Study Design**

The safety and effectiveness of the ADVIA Centaur® HBsAg and ADVIA Centaur® HBsAg Confirmatory assays was determined by a laboratory study consisting of the following:

- A study of prospectively obtained samples from patients who are either at risk for hepatitis B virus (HBV) infection (at least one risk factor indicated on the patient's case report form (CRF)), exhibiting signs and/or symptoms of HBV infection (at least two signs/symptoms indicated on the patient's CRF), or undergoing dialysis. These samples were tested using FDA approved or licensed HBV serological assays and their HBV status classified on the basis of the HBV serological marker results (HBV surface antigen (HBsAg), HBV e antigen (HBeAg), anti-HBV core antigen IgM (anti-HBc IgM) total anti-HBV core antigen (total anti-HBc), anti-HBe antigen (anti-HBe), and total anti-HBsAg (anti-HBs) – this testing was considered the reference testing) and the ADVIA Centaur® HBsAg assay at the clinical trial sites.
- A study of retrospectively collected samples, obtained from a commercial vendor, from HBV acutely infected and HBV chronically infected patients. Vendor assignment of HBV acute samples was based upon positive HBsAg and anti-HBc IgM assay results. Vendor assignment of HBV chronic samples was based upon the individual having positive HBsAg results for at least six months. Vendor assignment was verified by HBV marker testing at the clinical sites. These samples were tested with both the ADVIA Centaur® HBsAg assay and a reference HBsAg assay at the clinical trial sites.
- A study of prospectively obtained prenatal samples to determine the use of the ADVIA Centaur® HBsAg assay for prenatal testing. This population included pregnant women in the 1st, 2nd, and 3rd trimesters. These samples were tested with both the ADVIA Centaur® HBsAg assay and a reference HBsAg assay at the clinical trial sites.
- A study of retrospectively collected HBV seroconversion panels obtained from a commercial vendor. These panels were tested with both the ADVIA Centaur® HBsAg assay and a reference HBsAg assay at the clinical trial sites.
- A precision and reproducibility study in which a specimen panel was assayed over several days, at multiple clinical trial sites, and using multiple ADVIA Centaur® HBsAg assay reagent lots. The results were analyzed to derive precision estimates.

These studies are described in more detail below.

### **Gender Bias**

The total ratio of men versus women in the high risk, signs and symptoms, and dialysis prospective study was 39.9% male and 60.1% female. It is considered that this is reflective of the underlying distribution of the disease for each given age group, ethnic group, stage of disease, and the inclusion of a specific prenatal study. If the prenatal study population is removed the distribution for males is 54% and females 46%, which is a more equal gender distribution. There appeared to be no selection bias on the basis of gender identified during the review process other than those specimens which were retrospectively selected and the prenatal prospective population.

There appeared to be no difference in the safety and effectiveness of the device based on gender. This device appeared to have a similar effectiveness between men and women.

## Summary of Safety and Effectiveness

### Demographic Data

2740 patient samples were with the ADVIA Centaur® HBsAg assay. The following results classified by gender and age range were obtained:

<b>Bayer ADVIA Centaur® HBsAg Assay</b>							
<b>Distribution of High Risk, Signs and Symptoms, Dialysis, and Prenatal Population</b>							
<b>by Age Group and Gender</b>							
<b>All Testing Sites</b>							
Age (years)	Gender	Positive <sup>a</sup>		Nonreactive <sup>b</sup>		Total	
		N	%	N	%	N	%
0-9	Male	0	--	0	--	0	--
	Female	0	--	0	--	0	--
	Overall	0	--	0	--	0	--
10-19	Male	1	14.3	6	85.7	7	6.6
	Female	0	--	99	100	99	93.4
	Overall	1	0.9	105	99.1	106	100
20-29	Male	6	7.1	78	92.9	84	14.7
	Female	7	1.4	479	98.6	486	85.3
	Overall	13	2.3	557	97.7	570	100
30-39	Male	18	9.2	178	90.8	196	32.7
	Female	16	4.0	388	96.0	404	67.3
	Overall	34	5.7	566	94.3	600	100
40-49	Male	35	9.1	350	90.9	385	54.5
	Female	8	2.5	314	97.5	322	45.5
	Overall	43	6.1	664	93.9	707	100
50-59	Male	29	10.1	259	89.9	288	58.2
	Female	5	2.4	202	97.6	207	41.8
	Overall	34	6.9	461	93.1	495	100
60-69	Male	9	10.3	78	89.7	87	46.5
	Female	1	1.0	99	99.0	100	53.5
	Overall	10	5.4	177	94.7	187	100
≥70	Male	4	8.9	41	91.1	45	61.6
	Female	0	--	28	100	28	38.4
	Overall	4	5.5	69	94.5	73	100
Unknown	Male	0	--	1	100	1	50.0
	Female	0	--	1	100	1	50.0
	Overall	0	--	2	100	2	100
Total	Male	102	9.3	991	90.7	1093	39.9
	Female	37	2.2	1610	97.8	1647	60.1
	Overall	139	5.1	2601	94.9	2740	100

a Samples with an Index Value  $\geq 1.00$  that were confirmed positive

b Samples with an Index Value  $< 1.00$  and initially reactive samples that did not confirm as positive

### Data Analysis and Results

#### Prospective Study

The prospective study population for the ADVIA Centaur® HBsAg assay and the ADVIA Centaur® HBsAg confirmatory assay consisted of 2740 patients. Of these 2740 patients, 965 patients (35.2%) were from a population considered at risk for hepatitis (high risk) due to lifestyle, behavior, occupation, or known exposure events, 847 patients (30.9%) were from the population of individuals exhibiting signs and/or symptoms of hepatitis infection (signs and

## Summary of Safety and Effectiveness

symptoms), 212 patients (7.7%) were from the dialysis population, and 716 patients (26.1%) were from the prenatal population. The prenatal population included serum samples from healthy, pregnant women in their first trimester (149 of 716 patients [20.8%]), second trimester (272 of 716 patients [38.0%]), or third trimester (295 of 716 patients [41.2%]) of pregnancy. The prospective study population was 38.4% Hispanic, 31.8% Caucasian, 22.6% Black, 2.9% Asian, and 4.3% from unknown or other ethnicity. The majority of patients were female (60.1% female and 39.9% male). The mean age was 41.0 years (range of 12 to 82 years). Patients in the prospective study population were from the following geographic regions: Florida (37.8%), Texas (33.8%), New York (22.2%), and California (6.2%).

The HBV disease classification for each patient in the high risk, signs and symptoms, and dialysis populations (2024 total) was determined by serological assessment using resultant hepatitis marker profiles obtained from results of commercially available, FDA-approved assays, considered the reference assays. Testing of the specimens occurred at each study site. The individual ADVIA Centaur® HBV assay result was compared to the reference HBsAg assay result and to the patient classification determined by the six HBV serological marker combinations. No patients were excluded from the complete study set due to incomplete reference HBV serological results. Disease classification for each individual was based only on the HBV serological marker results, and was not affected by additional laboratory or clinical information. Results for HBsAg were based on the results of HBsAg neutralization testing for both the ADVIA Centaur® HBsAg assay and the reference assay. The unique reference marker patterns observed using the ADVIA Centaur® HBsAg assay are presented in the following table.

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<b>Bayer ADVIA Centaur® HBsAg Assay Classification by HBV Reference Markers (All Testing Sites)</b>						
<i>HBV Classification</i>	<i>HBV Reference Markers</i>					
	<i>HBsAg</i>	<i>HBeAg</i>	<i>IgM Anti-HBc</i>	<i>Total Anti-HBc</i>	<i>Anti-HBe</i>	<i>Anti-HBs (&gt;10 mIU/mL)</i>
Acute	+	+	+	+	+	-
Acute	+	+	+	+	-	-
Acute	+	-	+	+	+	-
Chronic	+	+	-	+	+	-
Chronic	+	+	-	+	-	+
Chronic	+	+	-	+	-	-
Chronic	+	-	-	+	+	+
Chronic	+	-	-	+	+	-
Chronic	+	-	-	+	-	+
Chronic	+	-	-	+	-	-
Chronic	+	+	+	+	-	+
Early Recovery	-	-	+	+	+	+
Early Recovery	-	-	+	+	+	-
Early Recovery	-	-	+	+	-	+
Early Recovery	-	-	+	+	-	-
Early Recovery	-	-	-	+	+	-
Recovery	-	-	-	+	+	+
Recovery	-	-	-	-	+	+
Recovered	-	-	-	+	-	+
Recovered	-	-	-	+	-	-
HBV Vaccine Response	-	-	-	-	-	+
Not previously infected	-	-	-	-	-	-
Uninterpretable	+	-	-	-	-	+
Uninterpretable	+	-	-	-	-	-
Uninterpretable	-	+	-	-	-	+
Uninterpretable	-	+	-	-	-	-
Uninterpretable	-	-	+	-	-	-
Uninterpretable	-	-	-	-	+	-
Uninterpretable	-	+	-	+	-	+
Uninterpretable	-	+	-	+	-	-
Uninterpretable	-	+	-	+	+	+

+ = Reactive  
- = Nonreactive

Following the assignment of specimen classification, the HBsAg results (nonreactive and confirmed reactive) obtained using the ADVIA Centaur® method were compared with the nonreactive and confirmed reactive HBsAg results obtained using the reference method for each result category. The method comparison for patients in the high risk, signs and symptoms, and dialysis populations for all testing sites combined is presented in the following table.

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Bayer ADVIA Centaur® HBsAg Assay Method Comparison in High Risk, Signs and Symptoms, and Dialysis Population by HBV Classification ADVIA Centaur® HBsAg Assay vs. HBsAg Reference Assay All Testing Sites					
HBV Classification	Reference HBsAg Negative ADVIA Centaur® HBsAg Assay		Reference HBsAg Positive ADVIA Centaur® HBsAg Assay		Total <sup>a</sup>
	Positive	Nonreactive	Positive	Nonreactive	
	N	N	N	N	N
Acute	0	0	10	1	11
Chronic	0	0	109	2	111
Early Recovery	0	126	0	0	126
Recovery	1	210	0	0	211
Recovered	3	320	0	0	323
HBV Vaccine Response	0	384	0	0	384
Not Previously Infected	2	826	0	0	828
Uninterpretable	1	22	3	4	30
<b>Total</b>	<b>7</b>	<b>1888</b>	<b>122</b>	<b>7</b>	<b>2024</b>

a Total number of test results by HBV categories

The percent agreement between the ADVIA Centaur® HBV method and the reference assays for each specimen classification was performed, including the upper and lower 95% confidence intervals. The positive, negative, and overall percent agreements were calculated as follows:

Positive percent agreement:

$$\frac{\text{Number of ADVIA Centaur® HBsAg confirmed positive results in agreement with reference HBsAg}}{\text{Total number of reference HBsAg confirmed positive results}} \times 100$$

Negative percent agreement:

$$\frac{\text{Number of ADVIA Centaur® HBsAg nonreactive results in agreement with reference HBsAg}}{\text{Total number of reference HBsAg nonreactive results}} \times 100$$

Overall percent agreement:

$$\frac{\text{Number of ADVIA Centaur® HBsAg results in agreement with reference HBsAg}}{\text{Total number of reference HBsAg confirmed positive and nonreactive results}} \times 100$$

The percent agreement between the ADVIA Centaur® HBsAg assay and the reference HBsAg assay for the high risk, signs and symptoms, and dialysis populations across all testing sites is summarized in the following table.

## Summary of Safety and Effectiveness

<b>Bayer ADVIA Centaur® HBsAg Assay</b> <b>Percent Agreement and Confidence Intervals by HBV Classification in High Risk, Signs and Symptoms, and Dialysis Population</b> <b>ADVIA Centaur® HBsAg Assay vs. HBsAg Reference Assay</b> <b>All Testing Sites</b>				
HBV Classification	Positive Percent Agreement % (x/n) <sup>a</sup>	95% Exact Confidence Interval	Negative Percent Agreement % (x/n) <sup>b</sup>	95% Exact Confidence Interval
Acute	90.91 (10/11)	58.72 to 99.77	--	--
Chronic	98.20(109/111)	93.64 to 99.78	--	--
Early Recovery	--	--	100.00 (126/126)	97.11 to 100.00
Recovery	--	--	99.53 (210/211)	97.39 to 99.99
Recovered	--	--	99.07 (320/323)	97.31 to 99.81
HBV Vaccine Response	--	--	100.00 (384/384)	99.04 to 100.00
Not Previously Infected	--	--	99.76 (826/828)	99.13 to 99.97
Uninterpretable	42.86 (3/7)	9.90 to 81.59	95.65 (22/23)	78.05 to 99.89
Overall	94.57 (122/129)	89.14 to 97.79	99.63 (1888/1895)	99.24 to 99.85

- a x = the number of ADVIA Centaur® HBsAg results that are confirmed positive in agreement with the reference HBsAg confirmed positive results; n = the total number of reference HBsAg results that are confirmed positive
- b x = the number of ADVIA Centaur® HBsAg results that are nonreactive in agreement with the reference HBsAg; n = the total number of reference HBsAg results that are nonreactive

### **Retrospective HBV Infected (acute and chronic stages of infection) Study**

A retrospective study was conducted using commercially obtained specimens, 49 well-characterized samples from patients diagnosed with acute HBV and 104 well-characterized samples from patients with chronic HBV (patients who had a positive HBsAg result at least 6 months prior to sample collection). Samples were evaluated using the ADVIA Centaur® HBV method and the reference assay). Vendor assignment of disease status was verified by testing with HBsAg, Anti-HBc IgM, Anti-HBc Total, and Anti-HBs assays at the testing sites.

The method comparison for the acute and chronic retrospective population across all testing sites is presented in the following table.

<b>Bayer ADVIA Centaur® HBsAg Assay</b> <b>Method Comparison in Retrospective HBV Infected Population</b> <b>ADVIA Centaur® HBsAg Assay vs. HBsAg Reference Assay</b> <b>All Testing Sites</b>					
HBV Disease Classification	Reference HBsAg Negative		Reference HBsAg Positive		Total
	ADVIA Centaur® HBsAg Assay		ADVIA Centaur® HBsAg Assay		
	Positive	Nonreactive	Positive	Nonreactive	
	N	N	N	N	
Acute	0	0	49	0	49
Chronic	0	0	102	2	104
Total	0	0	151	2	153

## Summary of Safety and Effectiveness

The percent agreement between the ADVIA Centaur® HBsAg assay and the reference HBsAg assay for the retrospective acute and chronic HBV infected population is summarized by testing site in the following table.

<b>Bayer ADVIA Centaur® HBsAg Assay</b>					
<b>Percent Agreement and Confidence Intervals by Testing Sites in Retrospective HBV Population</b>					
<b>Bayer ADVIA Centaur® HBsAg Assay vs. HBsAg Reference Assay</b>					
Testing Site	Population	Positive Percent Agreement % (x/n) <sup>a</sup>	95% Exact Confidence Interval	Negative Percent Agreement % (x/n) <sup>b</sup>	95% Exact Confidence Interval
Testing Site 1	Acute	100 (14/14)	76.8 to 100	--	--
	Chronic	94.3 (33/35)	80.8 to 99.3	--	--
Testing Site 2	Acute	100 (35/35)	90.0 to 100	--	--
	Chronic	100 (35/35)	90.0 to 100	--	--
Testing Site 3	Acute	--	--	--	--
	Chronic	100 (34/34)	89.7 to 100	--	--
All Testing Sites	Acute	100 (49/49)	92.8 to 100	--	--
	Chronic	98.1 (102/104)	93.2 to 99.8	--	--

- a x = the number of ADVIA Centaur® HBsAg results that are positive in agreement with the reference HBsAg; n = the total number of reference HBsAg results that are positive
- b x = the number of ADVIA Centaur® HBsAg results that are nonreactive in agreement with the reference HBsAg; n = the total number of reference HBsAg results that are nonreactive

The above studies demonstrate that if used according to the procedural directions the ADVIA Centaur® HBsAg and the ADVIA Centaur® HBsAg Confirmatory assay should provide a meaningful result for the diagnosis of HBV infection.

### **Prospective Study in Pregnant Women**

Serum samples were prospectively collected from 716 healthy, pregnant women who were in the first, second, or third trimester of pregnancy. By testing these samples from pregnant women using the ADVIA Centaur® HBsAg Assay and the reference HBsAg assay, the performance of the ADVIA Centaur® HBsAg assay in identifying neonates who were at risk for HBV infection during the perinatal period was evaluated.

Results of HBsAg testing (repeatedly nonreactive and confirmed positive by neutralization testing) were compared between the ADVIA Centaur® HBsAg assay and the reference HBsAg assay for the prenatal population. This comparison for all testing sites combined is presented in the following table.

Summary of Safety and Effectiveness

Bayer ADVIA Centaur® HBsAg Method Comparison in Prenatal Population ADVIA Centaur® HBsAg Assay vs. HBsAg Reference Assay					
Population	Reference HBsAg Assay Negative		Reference HBsAg Assay Positive		Total N
	ADVIA Centaur® HBsAg Assay		ADVIA Centaur® HBsAg Assay		
	Positive N	Nonreactive N	Positive N	Nonreactive N	
1 <sup>st</sup> Trimester	0	148	1	0	149
2 <sup>nd</sup> Trimester	0	268	4	0	272
3 <sup>rd</sup> Trimester	0	290	5	0	295
All	0	706	10	0	716

The percent agreement between the ADVIA Centaur® HBsAg assay and the reference HBsAg assay for the prenatal population by pregnancy trimester is summarized for all sites in the following table.

Bayer ADVIA Centaur® HBsAg Percent Agreement and Confidence Intervals by Testing Sites in Prenatal Population ADVIA Centaur® HBsAg Assay vs. HBsAg Reference Assay				
Trimester	Positive Percent Agreement % (x/n) <sup>a</sup>	95% Exact Confidence Interval	Negative Percent Agreement % (x/n) <sup>b</sup>	95% Exact Confidence Interval
1 <sup>st</sup>	100 (1/1)	2.5 to 100	100 (148/148)	97.5 to 100
2 <sup>nd</sup>	100 (4/4)	39.8 to 100	100 (268/268)	98.6 to 100
3 <sup>rd</sup>	100 (5/5)	47.8 to 100	100 (290/290)	98.7 to 100
All	100 (10/10)	69.2 to 100	100 (706/706)	99.5 to 100

- a x = the number of ADVIA Centaur® HBsAg results that are confirmed positive in agreement with the reference HBsAg confirmed positive results; n = the total number of reference HBsAg results that are confirmed positive
- b x = the number of ADVIA Centaur® HBsAg results that are nonreactive in agreement with the reference HBsAg; n = the total number of reference HBsAg results that are nonreactive

The above study supports the use of the ADVIA Centaur® HBsAg Assay for prenatal screening.

**Seroconversion Study**

To demonstrate when the ADVIA Centaur® HBsAg assay would first detect HBsAg after initial infection six commercially obtained seroconversion panels were tested with the ADVIA Centaur® HBsAg assay and a reference HBsAg assay.

The table below lists the individual panel results.

## Summary of Safety and Effectiveness

Panel ID	HBsAg Positive Result From Initial Draw Date		Reference Assay vs ADVIA Centaur® Assay
	Reference Assay (Days)	ADVIA Centaur® Assay (Days)	Difference in Bleed Numbers*
1	51	51	0
2	42	42	0
3	19	19	0
4	12	9	+2
5	7	7	0
6	61	61	0

\* The difference in bleed numbers is relative to the reference assay. For example, a +2 means that the reference assay required 2 additional bleeds before reactivity was determined as compared to the time-point when ADVIA Centaur® assay confirmed positive.

Compared to the reference HBsAg assay, the ADVIA Centaur® HBsAg assay demonstrated efficacy for the detection of the appearance of HBsAg following HBV infection.

To demonstrate the ability of the ADVIA Centaur® HBsAg Assay to detect truly positive HBsAg samples at  $\geq 50$  index value the ranges of index values for repeatedly reactive samples in the ADVIA Centaur® HBsAg assay were compared to neutralization results from the ADVIA Centaur® HBsAg Confirmatory assay. These data are summarized in the following table.

ADVIA Centaur® HBsAg Assay	Repeat Reactive Results	ADVIA Centaur® HBsAg Confirmatory Assay Confirmed	95% Exact Confidence Intervals
Index Range	N	N (%)	
$\leq 50$	14	10 (71.40)*	41.9 to 91.6
$50 < 500$	27	27 (100)	87.2 to 100
$> 500$	102	102 (100)	96.4 to 100
Total	143	139 (97.20)	93.0 to 99.2

\* Neutralization testing not performed on 4 specimens.

The above data support the use of the  $\geq 50$  index cutoff for not performing neutralization testing for samples whose results fall within this range. The low specimen number within the range of 50 - <300 is justified based on the low number of specimens that would fall within this range. It is believed that if this specimen number were larger the ADVIA Centaur® HBsAg assay would have a lower 95% Exact confidence interval value of  $\geq 90\%$ .

There were 133 samples that were repeatedly reactive or had results  $\geq 50$  index using the ADVIA Centaur® HBsAg assay. These samples were tested for HBsAg neutralization using the ADVIA Centaur® HBsAg Confirmatory assay. The results of this testing, for all testing sites, by HBV classification are presented in the following table.

## Summary of Safety and Effectiveness

<b>Confirmatory Results for Reactive Samples by HBV Classification in High Risk, Signs and Symptoms, and Dialysis Populations (All Testing Sites)</b>				
<b>HBV Classification</b>	<b>ADVIA Centaur® HBsAg Assay</b>		<b>Reference EIA HBsAg Assay</b>	
	<b>Repeat Reactive (n)</b>	<b>Positive By Neutralization (n)(%)</b>	<b>Reference assay Percent agreement with ADVIA Centaur® (%)<sup>1</sup> (n/n)<sup>2</sup></b>	
Acute	10	10 (100)	100% (10/10)	69.2 to 100
Chronic	109	109 (100)	100% (109/109)	96.7 to 100
Early Recovery	0	0 (0/0)	NA	NA
Recovery	1	1 (100)	0% (0/1)	NA
Recovered	5	3 (60)	0% (0/3)	0.0 to 70.8
HBV Vaccine Response	0	0 (0/0)	NA	NA
Not Previously Infected	4	2 (50)	0% (0/2)	0.0 to 84.2
Uninterpretable	4	4(100)	75.0% (3/4)	19.4 to 99.4
<b>Total</b>	<b>133</b>	<b>129 (96.99)</b>	<b>94.57% (122/129)</b>	<b>89.1 to 97.8</b>

<sup>1</sup> The percentage of Reference EIA HBsAg positive by neutralization samples which were also positive by neutralization in the ADVIA Centaur® HBsAg assay.

<sup>2</sup> The number of samples which were positive by neutralization in the Reference EIA HBsAg assay over the number of samples which were positive by neutralization in the ADVIA Centaur® HBsAg assay.

### **Precision and Reproducibility Study**

The ADVIA Centaur® HBsAg assay precision and reproducibility study was performed at 3 external sites utilizing 2 reagent lots per site. A 5-member panel and controls were assayed in replicates of 5 on a single run per day over 6 days for each lot. The study was completed with a single calibration of the assay (one calibration interval). Standard deviation and percent CV were calculated for within run, between run, and total. The site-specific results are presented in the following table.

Summary of Safety and Effectiveness

Bayer ADVIA Centaur® HBsAg Assay Precision Estimates for All Testing Sites and Reagent Lots									
Panel Member	Mean ADVIA Centaur® HBsAg Index Value	Within Run <sup>a</sup>		Between Run <sup>b</sup>		Total <sup>c</sup>		No. of Observations	No. of Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
<b>Testing Site 1, Reagent Lot 85</b>									
1	0.090	0.000	NA	0.000	NA	0.000	NA	30	6
2	0.625	0.086	13.76	0.173	27.69	0.193	30.92	30	6
3	1.738	0.084	4.82	0.179	10.30	0.198	11.37	30	6
4	4.315	0.122	2.83	0.185	4.28	0.221	5.13	30	6
5	20.156	0.395	1.96	0.820	4.07	0.910	4.52	30	6
Negative Control	0.090	0.000	NA	0.000	NA	0.000	NA	30	6
Positive Control	4.460	0.112	2.51	0.351	7.86	0.368	8.25	30	6
<b>Testing Site 1, Reagent Lot 86</b>									
1	0.090	0.000	NA	0.000	NA	0.000	NA	30	6
2	0.558	0.058	10.32	0.128	22.99	0.141	25.20	30	6
3	1.556	0.070	4.49	0.244	15.71	0.254	16.34	30	6
4	3.932	0.088	2.24	0.337	8.57	0.348	8.86	30	6
5	19.163	0.349	1.82	0.926	4.83	0.990	5.16	30	6
Negative Control	0.090	0.000	NA	0.000	NA	0.000	NA	30	6
Positive Control	4.337	0.097	2.23	0.293	6.76	0.308	7.11	30	6
<b>Testing Site 2, Reagent Lot 87</b>									
1	0.090	0.000	NA	0.000	NA	0.000	NA	30	6
2	0.671	0.083	12.42	0.150	22.42	0.172	25.63	30	6
3	1.696	0.065	3.81	0.079	4.64	0.102	6.00	30	6
4	4.270	0.106	2.49	0.099	2.33	0.145	3.41	30	6
5	20.049	0.244	1.22	0.448	2.23	0.510	2.54	30	6
Negative Control	0.093	0.009	NA	0.014	NA	0.017	NA	30	6
Positive Control	4.742	0.110	2.32	0.261	5.50	0.283	5.97	30	6
<b>Testing Site 2, Reagent Lot 86</b>									
1	0.094	0.021	NA	0.018	NA	0.027	NA	29	6
2	0.764	0.062	8.15	0.106	13.86	0.123	16.08	30	6
3	1.758	0.070	4.00	0.145	8.25	0.161	9.17	30	6
4	4.127	0.129	3.13	0.281	6.80	0.309	7.48	30	6
5	18.889	0.276	1.46	0.821	4.35	0.866	4.59	30	6
Negative Control	0.189	0.061	NA	0.092	NA	0.111	NA	30	6
Positive Control	4.565	0.117	2.56	0.334	7.33	0.354	7.76	30	6

Summary of Safety and Effectiveness

Bayer ADVIA Centaur® HBsAg Assay Precision Estimates for All Testing Sites and Reagent Lots (continued)									
Panel Member	Mean ADVIA Centaur® HBsAg Index Value	Within Run <sup>a</sup>		Between Run <sup>b</sup>		Total <sup>c</sup>		No. of Observations	No. of Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
<b>Testing Site 3, Reagent Lot 87</b>									
1	0.090	0.000	NA	0.000	NA	0.000	NA	30	6
2	0.656	0.142	21.64	0.154	23.55	0.210	31.98	30	6
3	1.689	0.132	7.82	0.227	13.47	0.263	15.58	30	6
4	4.222	0.176	4.17	0.407	9.65	0.444	10.51	30	6
5	19.580	0.659	3.37	1.551	7.92	1.685	8.61	30	6
Negative Control	0.164	0.099	NA	0.029	NA	0.103	NA	25	6
Positive Control	4.798	0.254	5.30	0.300	6.24	0.393	8.19	25	6
<b>Testing Site 3, Reagent Lot 85</b>									
1	0.096	0.031	NA	0.026	NA	0.040	NA	28	6
2	0.948	0.066	6.92	0.251	26.48	0.259	27.36	30	6
3	2.085	0.131	6.27	0.222	10.64	0.257	12.35	30	6
4	4.865	0.251	5.17	0.421	8.66	0.491	10.08	30	6
5	21.912	0.740	3.38	1.216	5.55	1.424	6.50	30	6
Negative Control	0.174	0.074	NA	0.124	NA	0.145	NA	30	6
Positive Control	4.934	0.287	5.82	0.224	4.54	0.364	7.38	30	6

a Variability of the assay performance within day (from replicate to replicate).

b Variability of the assay performance between days (from day to day).

c Variability of the assay performance combining the effects of within day and between days.

CV = Coefficient of variance

NA = not applicable

Note: 5 replicates per panel in 1 run per day for 6 days.

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The data from all 3 sites and from all 3 reagent lots were combined to achieve 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.

<b>Bayer ADVIA Centaur® HBsAg Assay</b>												
<b>Reproducibility</b>												
<b>Between Testing Sites and Between Reagent Lots Estimates</b>												
<b>(Across All Reagent Lots and All Testing Sites)</b>												
Panel Member	Mean ADVIA Centaur® HBsAg Index Value	Within Run <sup>a</sup>		Between Run <sup>b</sup>		Between Testing Site <sup>c</sup>		Between Lot <sup>d</sup>		Total <sup>e</sup>		Number of Observations
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	
1	0.09	0.015	NA	0.000	NA	0.001	NA	0.000	NA	0.015	NA	177
2	0.70	0.088	12.44	0.066	9.37	0.153	21.77	0.000	0.00	0.188	26.77	180
3	1.75	0.096	5.49	0.076	4.36	0.160	9.13	0.074	4.25	0.215	12.27	180
4	4.29	0.155	3.62	0.124	2.90	0.232	5.41	0.226	5.28	0.380	8.87	180
5	19.96	0.482	2.42	0.415	2.08	0.726	3.64	0.861	4.31	1.294	6.48	180
Negative Control	0.13	0.055	NA	0.019	NA	0.059	NA	0.000	NA	0.083	NA	175
Positive Control	4.63	0.177	3.83	0.112	2.42	0.212	4.57	0.060	1.30	0.304	6.56	175

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

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

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

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

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

CV = Coefficient of variance

NA = Not applicable

Note: 5 replicates per panel in 1 run per day for 6 days

### Interpretation of Clinical Studies

The following pattern of results interpretation was established on the basis of information collected from the clinical studies for the ADVIA Centaur® HBsAg assay:

- Samples with an Index Value of less than 1.00 are considered nonreactive (negative) for HBsAg.
- Samples with an Index Value of greater than or equal to 1.00 but less than or equal to 50 are considered initially reactive for HBsAg. Perform repeat testing in duplicate and /or supplemental testing on these samples.
- Heparin anticoagulants have been shown to reduce the Index values in some samples near the assay cut off. High negative results (0.70 – 0.99 Index) obtained on samples collected with lithium or sodium heparin anticoagulant should be interpreted accordingly. Additional testing is required including other HBV markers and supplemental tests.
- After repeat testing, if two of the three results are nonreactive (negative), the sample is considered negative for HBsAg.
- After repeat testing, if at least two of the three results are reactive, the sample is considered repeat reactive for the presence of HBsAg. If a repeatedly reactive result is confirmed by supplemental tests, such as the ADVIA Centaur® HBsAg Confirmatory assay, the sample is positive for HBsAg.
- If the sample is greater than 50, the specimen is positive for HBsAg by the

ADVIA Centaur® HBsAg assay.

**Device Failures and Replacements**

During the clinical studies there were no reported failures and/or replacements.

**XI. CONCLUSIONS DRAWN FROM THE STUDIES**

Multicenter studies were conducted in the US. The ADVIA Centaur® HBsAg assay performed with analytical sensitivity, analytical specificity, and positive agreement and negative agreement to reference methods, i.e., current commercially available FDA licensed or approved assays.

- Hepatitis B virus classification using the prospective study population showed 31 unique reference marker patterns. The overall positive and negative percent agreement between the ADVIA Centaur® HBV method and the reference assay was reasonable in the high risk, signs and symptoms, and dialysis populations combined.
- For the prenatal population, the overall positive and negative percent agreement between the ADVIA Centaur® HBV method and the reference assay was reasonable in all the trimesters tested.
- In the HBV infected acute and chronic retrospective population, the overall positive percent agreement was acceptable. As all samples were reference method positive, there is no negative percent agreement calculation.
- The ADVIA Centaur® HBsAg Confirmatory assay showed positive neutralization for 97.0 percent of samples that were repeatedly reactive by the ADVIA Centaur® HBsAg assay and 94.6 percent agreement with the reference assay for samples that were repeatedly reactive by the ADVIA Centaur® HBsAg assay for the high risk, signs and symptoms, dialysis, and prenatal populations combined.
- The ability of the ADVIA Centaur® HBsAg assay to detect HBV infection shortly after initial HBV infection was demonstrated with the seroconversion panel evaluation. When the ADVIA Centaur® HBsAg result was compared to the reference assay results the detection of the first reactive specimen was similar to that of the reference method.
- Precision and reproducibility of the ADVIA Centaur® HBsAg assay was acceptable with minor variability from run to run, day to day, or reagent lot to reagent lot.
- Paired Matrix Study results supported the use of human serum, EDTA plasma, and lithium heparin plasma specimens for testing in the ADVIA Centaur® HBsAg assay. The use of heparin anticoagulants required an adjustment of the assay cutoff for these specimens.

The results of the non-clinical and clinical studies indicate that the ADVIA Centaur® HBsAg and ADVIA Centaur® HBsAg Confirmatory assays can be used safely and

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effectively for the qualitative *in vitro* determination of HBsAg in human serum and plasma. The ADVIA Centaur® HBsAg and ADVIA Centaur® HBsAg Confirmatory assays may be used with other HBV serological markers to define the clinical status of patients known to be infected with HBV or with other HBV, HAV, and HCV assays to form a panel for the diagnosis of patients presenting with symptoms of acute or chronic viral hepatitis. In addition, the ADVIA Centaur® HBsAg and ADVIA Centaur® HBsAg Confirmatory assays can be used safely and effectively for the identification of neonates who are at risk for HBV infection during the perinatal period.

### **RISK BENEFIT ANALYSIS**

As a diagnostic test, the ADVIA Centaur® HBsAg 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 evaluations.

The potential risks encountered with *in vitro* diagnostic tests 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 individual tested.

The rate of false positivity and false negativity for the ADVIA Centaur® are within acceptable limits compared to the reference assay. It has been shown that the device has no demonstrable cross-reactivity with the viruses or organisms tested that may cause clinical hepatitis.

### **SAFETY**

Based on the results of the preclinical and clinical laboratory studies, the ADVIA Centaur® HBsAg assays, when used according to the provided directions and in conjunction with other serological and clinical information, should be safe and pose minimal risk to the patient due to false test results.

### **EFFECTIVENESS**

The effectiveness of the ADVIA Centaur® HBsAg has been demonstrated for use in determining if HBsAg is present in an individual's serum or plasma. A reasonable determination of effectiveness of the ADVIA Centaur® HBsAg assays for aiding in the diagnosis of acute and chronic HBV infection and prenatal screening has been demonstrated.

## XII. PANEL RECOMMENDATION

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

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### XIII. **CDRH DECISION**

FDA issued an approval order on May 26, 2005.

The applicant's manufacturing facility was inspected on May 11, 2004 (New York) and April 28, 2004 (Massachusetts) and was found to be in compliance with the Quality System Regulation (21 CFR 820).

### XIV. **APPROVAL SPECIFICATIONS**

Directions for Use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.