SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hepatitis B Virus e Antigen (HBeAg) Assay

Device Trade Name: ADVIA Centaur®HBeAg Assay
ADVIA Centaur®HBeAg Quality Control Material

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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P090024

Date of FDA Notice of Approval: October 11, 2011

Expedited: Not Applicable

II. INDICATIONS FOR USE

ADVIA Centaur® HBeAg Assay

The ADVIA Centaur® HBeAg Assay is an *in-vitro* diagnostic immunoassay for the qualitative determination of the hepatitis B e antigen (HBeAg) in human serum and plasma (potassium EDTA, lithium or sodium heparin) from individuals who have signs and symptoms of hepatitis or who may be at risk for hepatitis B virus (HBV) infection using the ADVIA Centaur® and ADVIA Centaur®XP systems. This assay, in conjunction with other serological and clinical information, is intended only for the determination of chronic infection with hepatitis B virus.

ADVIA Centaur® HBeAg Quality Control Material

The controls are used for monitoring the performance of the HBeAg Assay on the ADVIA Centaur® Systems. The performance of the HBeAg quality control material has not been established with any other HBeAg assay.

III. CONTRAINDICATIONS

The contraindications can be found on the ADVIA Centaur®HBeAg Assay and Quality Control Material labeling.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ADVIA Centaur®HBeAg Assay and Quality Control Material labeling.

V. DEVICE DESCRIPTION

A. Principles of the procedure: The ADVIA Centaur HBeAg Assay is an antibody sandwich (antibodies bridged by an antigen present in a sample) immunoassay using a 2-step, single-wash format. The ADVIA Centaur HBeAg ReadyPack primary reagent pack contains anti-HBe monoclonal antibody. The Solid Phase contains streptavidin-coated microparticles preformed with biotinylated anti-HBe Monoclonal antibody and is used to capture HBeAg from patient sample in first step. The Lite Reagent containing the anti-HBe monoclonal antibody labeled with acridinium ester is used in second step. The sample is incubated with the Ancillary Reagent. During the first step incubation, HBe antigen in the sample binds with anti-HBe monoclonal antibody. The Solid Phase and Lite Reagent are mixed in the next step. Any unbound HBeAg from the sample in the first step is bound by the Lite Reagent containing anti-HBe monoclonal antibody in the second step. After a wash step, the Reagent mixture is flashed by the addition of acid followed by base. The amount of relative light units (RLUs) detected by the system shows the amount of HBeAg activity present in the patient sample. Refer to the operator manual.

B. Kit configuration and components: The ADVIA Centaur HBeAg detection Assay kit is comprised of the following components:

1. A ReadyPack® primary reagent pack contains 50 tests and is composed of 3 reagents:

   - Solid Phase - Streptavidin-coated paramagnetic microparticles preformed with biotinylated mouse monoclonal anti-HBe (1 mg/L) in protein buffer, surfactant, sodium azide (14 mL/package)
   - Lite Reagent - Acridinium ester conjugated mouse monoclonal anti-HBe in protein buffer, surfactant, sodium azide (<0 1 %), preservatives (6 mL/package)
   - Ancillary Reagent - Non-magnetic latex particles in buffer with surfactant, sodium azide (< 0 1 %), and preservatives (6 mL/package)

2. ADVIA Centaur HBeAg Master Curve card.

3. Calibrators: Calibrators are composed of BSA buffer, preservatives, and rHBeAg diluted in a BSA buffer, sodium azide (< 0 1%), preservatives (2mL/vial). A kit includes 1 vial of low and 1 vial of high HBeAg Calibrator.

4. ADVIA Centaur HBeAg Calibrator Assigned Value card.

Reagents required but not provided in the kit:

1. ADVIA Centaur HBeAg negative and positive quality controls are re-calcified human plasma containing sodium azide (< 0 1 %), preservatives (10 mL/vial).

2. ADVIA Centaur Wash 1 contains Phosphate buffered saline with sodium azide (< 0.1 %) and surfactant; 2 x1500 mL/pack or 2 x2500 mL/pack.

3. ADVIA Centaur Probe Wash 3 contains sodium hypochlorite (0 5%), sodium hydroxide (< 0 5%), pH 11; 50 mL/pack.

C. Assay Procedure: The ADVIA Centaur HBeAg Assay is an antibody sandwich (antibodies bridged by an antigen present in a sample) two wash immunoassay. The solid phase contains a preformed complex of streptavidin-coated microparticles and biotinylated anti-HBe monoclonal antibody and is used to capture HBeAg from patient sample. Lite reagent contains anti-HBe monoclonal antibody labeled with acridinium ester and is used to detect HBeAg in the sample.

The system will wash the reagent probe with Probe Wash 3 (PW3) to mitigate potential interference between the ADVIA Centaur HBeAg Assay and other assays. Solid phase is added to the sample, followed by Lite reagent. Antibody-antigen complexes form if HBeAg is present in the sample.

The system automatically performs the following steps:

- dispenses 100 µL of sample into a cuvette and incubates for 6 minutes at 37°C
- dispenses 100 µL of ancillary reagent and 250 µL of solid phase reagent and incubates for 18 minutes at 37°C
- washes the cuvette with Wash 1
- dispenses 100 µL of Lite reagent, incubates the mixture for 18 minutes at 37°C
- separates the Solid Phase from the mixture and aspirates the unbound reagent
- washes the cuvette with Wash 1
- dispenses 300 µL each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction
- reports results according to the selected option, as described in the system operating instructions or in the online help system

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

D. Master Curve Calibration

The ADVIA Centaur HBeAg Assay requires a Master Curve calibration when using a new lot number of Lite Reagent, Solid Phase, and Ancillary Reagent. For each new lot number of Lite Reagent, Solid Phase, and Ancillary Reagent, the Master Curve values are entered on the system using the barcode reader or keyboard. The Master Curve card contains the Master Curve values.

E. Calibration and Controls

For calibration of the ADVIA Centaur HBeAg Assay, the HBeAg Calibrators provided with each kit are used. The ADVIA Centaur HBeAg assay requires a 2-point calibration (low and high).

The controls are used for monitoring the performance of the HBeAg Assay on the ADVIA Centaur® Systems. The performance of the HBeAg quality control material has not been established with any other HBeAg assay.

F. Interpretation of Results: The ADVIA Centaur system reports HBeAg results in Index Values and as reactive (positive), nonreactive (negative), or as needing retest.

If the controls are out of range, sample results are invalid and must be repeated

- **Nonreactive**: Samples with an initial value < 0.80 Index Value. The patient is considered nonreactive (negative) for HBeAg. No further testing is necessary.

- **Reactive**: Samples with an initial value > 1.2 Index Value. The patient is considered reactive (positive) for HBeAg. No further testing is necessary.

- **Retest Zone**: Samples with an initial value > 0.80 and < 1.2 Index Value. If results are within the retest zone after initial testing, samples are to be retested in duplicate. After retesting, if 3 results are available and 2 results are Index Value
  > 1.00, then the sample is considered to be reactive (positive). If 3 results are available and 2 results are < 1.0 Index Value, then the sample is considered to be nonreactive (negative).

If the controls are out of range, sample results are invalid and must be repeated.

Very highly reactive samples with HBeAg levels may generate a Signal 4 error. If you observe a Signal 4 error, dilute the sample and retest.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently several FDA approved *in vitro* diagnostic tests for serological markers of hepatitis B virus (HBV) infection which, when used in conjunction with a patient's medical history, clinical examination and other laboratory findings, can

be used for diagnosis of HBV infection. For HBeAg serological marker, there are currently three other FDA approved HBeAg devices.

VII. MARKETING HISTORY

The ADVIA Centaur HBeAg Assay is currently being marketed internationally in accordance with section 802 of the FD&C Act. The following table provides the list of countries where the product is distributed currently:

BRAZIL
CANADA
MALAYSIA
SINGAPORE
PHILIPPINES
JAPAN
HONG KONG
KOREA
AUSTRALIA
NEW ZEALAND
SOUTH AFRICA
AUSTRIA
CZECH REPUBLIC
TURKEY
DENMARK
FINLAND
IRELAND
NETHERLANDS
NORWAY
POLAND
UNITED KINGDOM
RUSSIA
BELGIUM
FRANCE
GREECE
ITALY
PORTUGAL
SPAIN
SWITZERLAND
GERMANY

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 device.

When used according to the instructions in the package insert, there are no known direct adverse effects of this device on the health of the user. Standard good laboratory practices are considered sufficient to minimize risks to the end 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.

The diagnosis of HBV infection requires the evaluation of the patient's blood for HBsAg, hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb). The HBeAg assay is not usually required in the initial diagnosis of HBV infection. However, it may be used as an aid in guiding antiviral therapy for patients that are chronically infected with HBV, in conjunction with HBV viral load test result. Seroconversion (i.e., conversion from HBeAg positive to HBeAg negative, followed by conversion from hepatitis B e antibody [anti-HBe] negative to anti-HBe positive) usually predicts long-term reduction in viral replication and may be used as a response marker to antiviral therapy. Therefore, repeatedly false negative or false positive results have the potential to lead to inappropriate treatment decisions.

A false negative HBeAg result may lead to prematurely withdrawer of antiviral therapy. A false reactive (false positive) result may lead to unnecessary prolonged antiviral therapy. Under these circumstances, there may be a safety concern for the patient. However, for chronic HBV patients who are on antiviral therapy, suppression of HBV DNA levels as measured by HBV viral load tests is often used as an end point of treatment.

The risk of incorrect test results is inherent with all *in vitro* diagnostic products. Therefore, the above potential risks are not unusual in the laboratory setting.

IX. SUMMARY OF PRECLINICAL STUDIES

All studies were performed using the ADVIA Centaur and ADVIA Centaur XP Systems.

A. Antibody Characterization

There were two monoclonal antibodies used in the ADVIA Centaur HBeAg Assay. Both antibodies were purchased from BiosPacific. BiosPacific clone A34152404P was used in preparation of the AE conjugate. BiosPacific clone A34162404P was used in preparation of the biotin conjugate. Both antibodies were characterized by gel electrophoresis and western blot analysis. Both

antibodies showed similar banding patterns with pI values typical of monoclonal antibodies.

B. Cut-off

The cut-off was established with internal studies measuring 622 samples i.e., 218 HBV positive patients, and 404 HBV negative donors. In the negative population, the 404 samples were comprised of 203 clinical specimens (i.e. hospital or clinic patients) and 201 normal (asymptomatic) donor specimens. The cutoff for the ADVIA Centaur HBeAg assay was verified based on results of Receiver- Operator characteristics (ROC) Curve and clinical agreement generated from clinical studies. The cut-off was determined 1.0 Index Value.

C. Potentially Cross-Reacting Subgroups

The ADVIA Centaur HBeAg Assay was evaluated for potential cross-reactivity with other viral infections and disease state specimens. The majority of the samples tested in this analytical specificity study were characterized based on the relevant antibody markers rather than the relevant antigen markers. Potential cross-reactants from 13 groups, totaling 130 specimens were assayed. The activity of cross reactant specimens were confirmed by the vendor using the FDA approved methods. Two lots of reagents (Pilot 1 and 2) were used on two Centaur instruments (DK and P47). The HBeAg status of each specimen was verified using a HBeAg reference assay. The following results were obtained using the ADVIA Centaur® HBeAg assay:

Description	N	Centaur HBeAg		Reference HBeAg In-house
		Negative	Reactive	Negative
Hepatitis A (HAV)	10	10	0	10
Hepatitis C (HCV)	10	10	0	10
Autoimmune Disease	10	10	0	10
Epstein-Barr Virus (EBV) IgM	10	10	0	10
Herpes Simplex Virus (HSV) IgM	10	10	0	10
Syphilis IgM	10	10	0	10
Human Immunodeficiency Virus (HIV-1)	10	10	0	10
Varicella Zoster Virus (VZV) IgM	10	10	0	10
Rubella IgM	10	10	0	10
Cytomegalovirus (CMV) IgM	10	10	0	10
Toxoplasma	10	10	0	10
Flu Vaccine Recipients	10	10	0	10
Human anti-mouse antibody (HAMA)	10	10	0	10
Total	130	130	0	130

D. Endogenous Interfering Substances

The ADVIA Centaur HBeAg Assay was evaluated for endogenous interference according to the Clinical and Laboratory Standards Institute (CLSI) EP7-A2. One negative and 2 samples spiked with HBeAg at low (Index 1.6) and medium (Index 6) were tested with and without interferents using one reagent lot on 2 Centaur instruments in replicates of six. The following substances were tested in all four matrices:

Hemoglobin: 250 mg/dL and 500 mg/dL
Intralipid: 1000 mg/dL and 3000 mg/dL
Unconjugated bilirubin: 20 mg/dL and 40 mg/dL
Conjugated bilirubin: 20 mg/dL and 60 mg/dL
Low Protein (Human Albumin): 3.5 g/dL
High Protein (Human Albumin): 12 g/dL
Biotin: 25 mg/dL and 100 mg/dL

The percent change in the measured HBeAg Index (concentration) was calculated as follows:

% Difference = ((Observed Conc- Expected Conc)/Expected Conc) x 100

The ADVIA Centaur HBeAg Assay showed a <10% interference from each substance. The observed results met the acceptance criteria of <15% of a change in HBeAg clinical interpretation. The studies showed no effect of potential interferents on the performance of the ADVIA Centaur HBeAg Assay.

Additionally, the effect of potential interferents (bacterial and recombinant viral antigens) on the performance of the ADVIA Centaur HBeAg Assay was determined using methods based on Clinical and Laboratory Standards Institute (CLSI) EP7-A2). All interfering substances were spiked into HBeAg negative and positive serum and plasma specimens. The studies showed no effect of potential interferents on the performance of the ADVIA Centaur HBeAg Assay. The table below shows a list of potential interferents spiked into the negative and positive specimens.

Spiked Material	Reactivity Before Spike	Reactivity After Spike
Negative serum spiked with bacterial antigens		
S. aureus 1000 CFU/mL	Non-reactive	Non-reactive
S. aureus 10,000 CFU/mL	Non-reactive	Non-reactive
P. aeruginosa 1000 CFU/mL	Non-reactive	Non-reactive
P. aeruginosa 10,000 CFU/mL	Non-reactive	Non-reactive
E. coli 1000 CFU/mL	Non-reactive	Non-reactive
E. coli 10,000 CFU/mL	Non-reactive	Non-reactive
HBeAg spiked positive serum with bacterial antigens		
S. aureus 1000 CFU/mL	Reactive	Reactive
S. aureus 10,000 CFU/mL	Reactive	Reactive
P. aeruginosa 1000 CFU/mL	Reactive	Reactive
P. aeruginosa 10,000 CFU/mL	Reactive	Reactive
E. coli 1000 CFU/mL	Reactive	Reactive
E. coli 10,000 CFU/mL	Reactive	Reactive
Negative serum spiked with viral antigens		
EBV 1 µg/mL	Non-reactive	Non-reactive
EBV 1 ng/mL	Non-reactive	Non-reactive
CMV 1 µg/mL	Non-reactive	Non-reactive
CMV 1 ng/mL	Non-reactive	Non-reactive
VZV 1 µg/mL	Non-reactive	Non-reactive
VZV 1 ng/mL	Non-reactive	Non-reactive
Rubella 1 µg/mL	Non-reactive	Non-reactive
Rubella 1 ng/mL	Non-reactive	Non-reactive
HBeAg spiked positive serum with viral antigens		
EBV 1 µg/mL	Reactive	Reactive
EBV 1 ng/mL	Reactive	Reactive
CMV 1 µg/mL	Reactive	Reactive
CMV 1 ng/mL	Reactive	Reactive
VZV 1 µg/mL	Reactive	Reactive
VZV 1 ng/mL	Reactive	Reactive
Rubella 1 µg/mL	Reactive	Reactive
Rubella 1 ng/mL	Reactive	Reactive

E. Analytical Sensitivity

An analytical sensitivity of the ADVIA Centaur HBeAg Assay was evaluated by preparing serial dilutions of the Paul Ehrlich Institute (PEI) in HBV negative plasma basepool to obtain concentration varying from 0.05 - 5 PEI IU/mL. The calculated concentration at endpoint was approximately 0.055, 0.46, and 0.05 Units/mL on three lots and one instrument. Linear regression was used to

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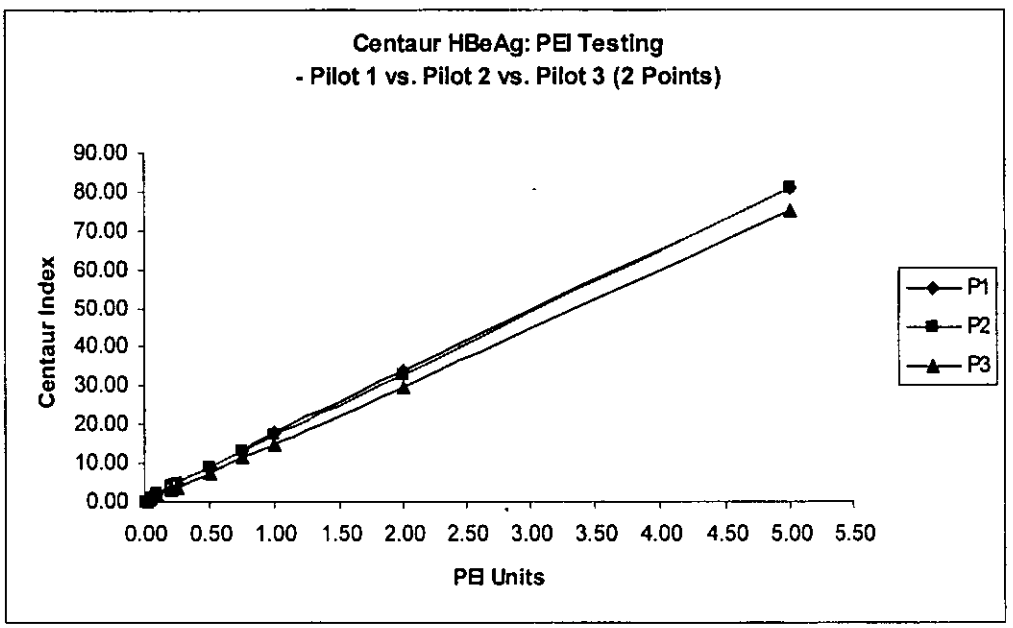
determine the concentration of PEI reference sample that corresponds to the ADVIA Centaur HBeAg cut-off (Index Value = 1.0). Centaur HBe Index Value 1.00 (cut-off) corresponded to approximately 0.055, 0.046, and 0.05 PEI IU/mL for Pilot 1, 2, & 3 reagents respectively. The PEI International Unit (IU) concentration at the ADVIA Centaur HBeAg Assay cut-off was less than 0.10 U/mL.



F. Hook Effect

Hook effect does not apply on the ADVIA Centaur HBeAg Assay because the assay is a monoclonal sandwich immunoassay and is a two wash assay. Any excess HBeAg in the sample not bound to capturing antibodies is washed out prior to the addition of detecting antibodies. Hook effect will not occur because there is no saturation of anti- HBe antibodies by the sample HBeAg.

G. Effects of Type of Collection Tube on Matrix Data

The effects of type of collection tube and different anticoagulants on assay performance were evaluated by testing donor samples collected in different collection tubes containing anticoagulants shown below.

Tube Type	Material
K_2EDTA	Glass/Plastic
Sodium Heparin	Glass/Plastic
Lithium Heparin	Glass/Plastic
SST	Glass/Plastic
Serum Red Top	Glass/Plastic

Of the 50 samples, 20 were left as negative. The other 30 samples were divided into two 15-member panels and spiked with HBeAg high-titer plasma. The first 15 were spiked to obtain Index values either close to the cut-off (Index 1.0) or at low reactive levels (Index between 1 and 10). The other 15 specimens were spiked to a target between 10 and 50 Index. Each sample was run in 3 replicates on one reagent lot and Index values determined. Index values were averaged and percent recovery calculated for the mean index value of the HBeAg positive/reactive samples for each tube type vs. control serum. In this study there was no change in clinical interpretation when samples were tested using different collection tubes when compared to samples collected in redtop serum tubes. In conclusion, these collection tubes are acceptable for use with the ADVIA Centaur HBeAg assay.

H. Calibrator and Control on-Board Stability Studies

A real time on-board stability studies of calibrators and controls was conducted using the Pilot lots of Calibrators and Controls. Stability of two pilot lot of calibrators (C1187L and C1197H) and control lots (K1109181N, K1109182P, and K1113082P lyophilizes) were tested at 0, 4, 8, and 24 hrs. Calibrators and controls were stored in sample cups that remained on-board Centaur (DE) and were tested at different intervals. HBeAg Index value recovery at time 0 was compared with other time points. HBeAg Pilot 3 (#105097) was used and each sample was run in 3 replicates.

The acceptance criteria for the calibrators and controls were within +/- 20% of baseline across time points. Negative control must remain negative (Index < 0.80)

The calibrator and control recoveries were within 10% of baseline to 24 hrs. Negative control remained negative from 0 to 24 hours. The ADVIA Centaur HBeAg Assay package insert includes 8 hours of Calibrator and Control on-board stability.

I. Sample Handling Studies

The sample handling studies were a series of experiments in which specimens collected in the sample matrices claimed as suitable for use in the ADVIA Centaur HBeAg method were subjected to potential stresses and then tested using the ADVIA Centaur HBeAg assay. Samples were subjected to freeze/thaw cycling and elevated temperature storage, and tested in comparison to a non-stressed control sample to determine the impact of the stress on assay accuracy. The sample handling studies were evaluated the effect of the following patient sample-handling conditions on ADVIA Centaur HBeAg Index Values:

- Extended time onboard the ADVIA Centaur® System

- Extended time in refrigerated (2 -8°C) storage
- Extended time at room temperature (25°C) storage
- Extended time in freezer (–20°C) storage
- Multiple freeze thaw (–20°C/2- 8°C) cycles

Samples were collected during in-house blood draws from healthy donors in serum and plasma collection tubes with a variety of anti-coagulants. Samples were spiked with HBeAg, aliquoted and placed in appropriate storage/stress conditions on the day of collection. Two samples were left unspiked. A baseline Index value for each sample was established by testing with the ADVIA Centaur HBeAg Assay on the day of collection. Each sample was run in triplicate. All percentage recoveries were calculated against the baseline (day 0) value. Results from the sample-handling studies supported the claims that samples can be subjected to the following HBeAg Assay:

- Samples can be kept onboard the Centaur system for at least 8 hours.
- Samples can be stored at room temperature for at least 24 hours
- Samples can be stored refrigerated (2-8°C) up to 7 days.
- Samples can be stored frozen (–20°C) for long term storage (1 year tested).
- Samples can be frozen and thawed up to 3 times.

J. Sample stability at 2-8^{0}C in Primary Tubes on Clot

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 HBeAg Index Value. Fresh samples were drawn from 5 healthy in-house donors into serum and plasma collection tube types. The specimens were centrifuged within the recommended time and an aliquot from each primary tube was placed in another container. Samples remained in the primary tubes on the clot or packed red cells and were stored at 2 – 8°C. The samples were tested at 0, 2, 4 and 7 days. HBeAg activity at day 0 was compared to the other time points. No negative samples showed any significant change. Overall the positive samples showed a change of less than 20% after 24 hours and clinical interpretation was consistent across all time points. Based on this study, samples can be stored in the primary collection tube for up to 7 days at 2 - 8°C.

K. Sample Processing – Time to Centrifugation

This study was undertaken to determine the effect of time to centrifugation on the HBeAg Index Value. Blood was drawn from four donors in house in each of the following tube types: Serum Red Top plastic and glass, SST plastic and glass, K2-EDTA plastic, Sodium Heparin plastic and glass, Lithium Heparin

plastic and glass. Four donors were spiked prior to centrifugation (normalized by gravimetric methods) with HBeAg positive plasma.

Each sample was centrifuged within 5 and 24 hours after draw and assayed.

The clinical status of the sample was the same regardless of time of centrifugation or tube type. In conclusion, in comparison with immediate centrifugation, sample processing by centrifugation up to 24 hours post draw does not result in significant changes in Index Value in the ADVIA Centaur HBeAg Assay.

L. Inverted Gel Barrier Collection Tubes

The effect of various inverted gel barrier collection tubes were tested for the performance of the ADVIA Centaur HBeAg Assay because these tube types sometimes become inverted during the transport to the clinical lab. This study was designed to determine if inverted gel barrier tubes have the same HBeAg Index activity as tubes that were not inverted. Blood samples were drawn from 9 healthy in-house donors using serum and plasma (lithium heparin and potassium EDTA) gel barrier (separator) collection tubes. Sample tubes were spiked with different amounts of anti-HBe positive plasma. Three donor tubes were left unspiked. The tubes were inverted, centrifuged, and an aliquot was taken. The tubes were then inverted 5 times and another aliquot was taken. The 2 aliquots were compared in the ADVIA Centaur HBeAg Assay. A total of 5 inversions of the barrier gel collection tube had no effect on the HBeAg Index Value for samples that were spiked with HBeAg plasma and for unspiked samples.

M. Reagent, Calibrator, and Control Real Time Stability Studies

Real-time stability studies were carried out using three lots of Centaur HBeAg 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 HBeAg reagents, calibrators, and controls.

N. Reagent Onboard Stability (OBS) Studies

Three lots of Centaur HBeAg reagents have undergone reagent OBS studies on 2 ADVIA Centaur systems. Onboard stability testing occurred at several checkpoints after the reagents were placed onboard. A fresh pack served as the control for each time-point. Index Value recovery within 15% (20% for the low calibrator) or 2 standard deviations of the fresh pack defined

acceptable performance. A calibration interval of 42 days was also evaluated using these results.

The on-board studies for the reagents supported 60 days OBS and a 30-day recalibration for the Centaur HBeAg reagents.

O. Reagent Shipping Stability Studies

Shipping studies for the ADVIA Centaur HBeAg Assay reagents indicated that the product tolerated 3 freeze/thaw/ cycles (-40°C to 2-8°C and) without aggregation of the solid phase and acceptable performance. Shipping studies also included 2-8°C to elevated temperature (30°C) cycling. These studies also tested for shipment of upside-down packs. ReadyPack reagents stored upside down tolerated up to 8 weeks in this position, although the recommended shipping condition will be upright at 2 to 8°C. The recommended shipping conditions are to ship the ReadyPack reagents in an upright position and stored at 2- 8°C.

P. Calibrator and Control Open Vial Stability Studies

The calibrator and control open vial use study examined the length of time the calibrator or control was stable once the vial was opened. Open vials were stored at the recommended storage conditions of 2 to 8°C. The open vials were sampled periodically up to 92 days post initial opening. Fresh (unopened) vials were evaluated at each time point to serve as controls.

The acceptance criteria for this study was dose recovery within 10% (or 2 standard deviations) of the Index obtained using a fresh vial. The study supported an open vial use lifetime of up to 92 days.

Q. Calibrator and Control Shipping Stability Studies

Shipping studies for the ADVIA Centaur Anti-HBe Assay calibrators and controls indicated that the product tolerated 3 freeze/thaw cycles (-40°C to 2-8°C and) with acceptable performance. Shipping studies also included 2-8°C to elevated temperature (30°C) cycling. The Centaur HBeAg Assay calibrators and controls should be stored and shipped at 2-8°C. The data demonstrate that calibrators and controls can perform according to specifications after freeze/thaw, but could not tolerate heat stressed treatments. Therefore, the recommended shipping for these components is 2-8°C in order to prevent any change in accuracy due to heat stress. The recommended shipping conditions are to ship the HBeAg calibrators and controls in an upright position and stored at 2 to 8°C.

R. Instrument Studies

Environmental Testing
The purpose of environmental testing was to assess ADVIA Centaur HBeAg Assay control recovery at the mean and extreme environmental conditions as specified in the ADVIA Centaur User's Guide. Each assay was 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 was then calculated.

ADVIA Centaur HBeAg Assay environmental testing data met the general specification of less than a 10% control recovery change over a 6°C ambient temperature change for samples near the cutoff. The studies demonstrated acceptable performance of the ADVIA Centaur HBeAg 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 HBeAg 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 HBeAg assay. For an interaction to be acceptable and therefore not require mitigation, there must be <5% difference in Index between test and control, or no statistically significant change in Index.

When Centaur HBeAg was tested to determine it's effect on other assays, Centaur HBeAg Lite Reagent (LR) and Solid Phase (SP) spiked into Centaur HBcT assay lite reagent (LR) and solid phase (SP) caused interference. Further testing to eliminate this interference by implementation of additional washes was performed. The implementation of up to three water washes did not mitigate the HBeAg LR and SP into HBcT SP and LR interference.

The HBeAg LR and SP into HBcT SP and LR interference was mitigated using a 0.5% bleach wash solution. The 0.5% bleach solution is manufactured as a Centaur reagent and has been given the designation "Probe Wash 3" or "PW3". When HBeAg and HBcT assays are run on the same Centaur, Probe Wash 3 washes the reagent probe before aspirating HBcT SP or HBcT LR in order to prevent HBeAg reagents from being carried over into the HBcT ready pack and causing interference. The PW3 wash is automatically implemented by the Centaur test definition ("TDef") software.
Similarly, when other Centaur assays were tested to determine their effect on the Centaur HBeAg assay, it was shown that the Centaur anti-HBe and HBcT

assays caused interference. This interference was mitigated using a 0.5% bleach wash solution "Probe Wash 3" or "PW3".

S. Microbial and Preservative Challenge Study

The ADVIA Centaur® HBeAg Assay consists of Ancillary Reagent, Lite Reagent, Solid Phase Reagent, Low Calibrator, High Calibrator, Negative Control and Positive Control. All reagents from one of the lots were sent to QA Microbiological Services Laboratory in Mishawaka, IN for microbial effectiveness testing. The shipped volume of each Reagent and Control was divided into 7 aliquots. Each aliquot was tested with a culture of one of the seven organisms. The tested organisms were *S. aureus, E. coli, P. aeruginosa, C. piscicola, C. albicans, P. niger, and P. species.* Samples from inoculated aliquot were plated once a week for 6 weeks and plate colonies counted to estimate CFU per mL. The pattern of CFU/mL change over time to each test organism was interpreted to determine effectiveness of reagent antimicrobial formulation for each of reagents tested and assigned an anti-microbial effectiveness category as defined by USP 28 NF [51] pg. 2242. The ADVIA Centaur® HBeAg Reagents were classified in the following categories:

ADVIA Centaur® HBeAg Ancillary Reagent - Class IV
ADVIA Centaur® HBeAg Lite Reagent - Class II
ADVIA Centaur® HBeAg Solid Phase Reagent - Class III
ADVIA Centaur® HBeAg High and Low Calibrator - Class III
ADVIA Centaur® HBeAg Plasma Negative and Positive Control - Class IV

T. Internal Precision

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

Precision studies were conducted using the samples that spanned the range of the assay including a low positive and high negative sample. The samples were prepared by spiking negative serum. The calibrators, controls and a panel of 5 spiked samples in serum were run on Centaur, two run per day, for 20 days in triplicate. Testing was performed from 3/20/10 through 4/27/10. Centaur HBeAg precision met the criteria of 10% CV within-run and 15% total CV for serum. There are no precision criteria for negative samples. The data are presented in the table below.

Internal Precision

Panel Members	Mean Index Value	Within Run SD	Within Run CV (%)	Between Run SD	Between Run CV (%)	Between Days SD	Between Days CV (%)	Total SD	Total CV (%)	Number of Observations
Control Negative	0.12	0.10	NA	0.11	NA	0.01	NA	0.15	NA	120
Control Positive	8.18	0.24	2.9	0.23	2.9	0.14	1.7	0.36	4.4	120
1	0.73	0.09	12.5	0.1	13.8	0	0	0.14	18.6	120
2	1.19	0.08	6.5	0.09	8	0.03	2.6	0.13	10.6	120
3	1.76	0.1	5.7	0.09	4.9	0.07	3.8	0.15	8.4	120
4	27.02	1.11	4.1	0.52	1.9	0.91	3.4	1.53	5.7	120
5	165.31	6.52	3.9	7.32	4.4	0	0	9.8	5.9	120

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A summary of the clinical study is presented below:

A multi-center prospective study was conducted to evaluate the clinical performance of the ADVIA Centaur HBeAg Assay. A study of prospectively obtained samples from patients who are either at risk for Hepatitis B (at least one risk factor indicated on the patient's CRF), exhibiting signs and/or symptoms of Hepatitis B infection (at least two signs/symptoms indicated on the patient's CRF) or undergoing dialysis. 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 HBeAg Assay and a reference HBeAg Assay at three clinical trial sites.

The study population for the ADVIA Centaur HBeAg assay consisted a total of 1744 patients. Of the 1744 samples, 1694 were collected prospectively and 50 were collected retrospectively. Of the 1694 prospectives, 935 patients (55.2%) were from the population considered at risk for hepatitis (high risk) due to lifestyle, behavior, occupation, or known exposure events, 654 patients (38.6%) were from the signs and symptoms population and 105 patients (6.2%) were from the dialysis population. A total of 50 retrospective specimens (50) were from chronic patients.

The study population was 25.1% Hispanic, 46.2% Caucasian, 17.5% Black, 6.5% Asian, and 4.8% from unknown or other ethnicity. The patients were nearly equally divided by sex (46.9% female, 51.8% male, and 1.4% unknown). The mean age was 43.6 years (range of 17 to 85 years). Patients in the study population were from the following geographic regions: Florida (40.5%), Texas (48.5%), California (5.6%), Vietnam (2.9%), and elsewhere (2.6%). The data to classify the hepatitis B status was not available for 16 (0.95%) of these patients. These patients have been excluded from subsequent analyses. In addition, 2 (0.1%) apparently contaminated samples were excluded.

The ADVIA Centaur HBeAg results for the prospective population for all sites combined by age group and gender are summarized in the following table:

Distribution of Study Population by Age Group and Gender (All Testing Sites)

Age Range	Gender	Reactive[a]		Nonreactive[b]		Total
Years		Number	(%)[c]	Number	(%)[c]	Number
0-16	Male	0		0		0
	Female	0		0		0
	Overall	0		0		0
17-20	Male	1	11.1	8	88.9	9
	Female	5	20.8	19	79.2	24
	Overall	6	18.2	27	81.8	33
21-29	Male	7	6.4	103	93.6	110
	Female	6	4.5	127	95.5	133
	Overall	13	5.3	230	94.7	243
30-39	Male	20	11.4	155	88.6	175
	Female	11	6.5	157	93.5	168
	Overall	31	9.0	312	91.0	343
40-49	Male	24	8.3	264	91.7	288
	Female	4	1.7	233	98.3	237
	Overall	28	5.3	497	94.7	525
50-59	Male	18	8.5	195	91.5	213
	Female	11	6.3	164	93.7	175
	Overall	29	7.5	359	92.5	388
60-69	Male	9	13.0	60	87.0	69
	Female	10	12.0	73	88.0	83
	Overall	19	12.5	133	87.5	152
>=70	Male	3	12.5	21	87.5	24
	Female	0	0.0	20	100.0	20
	Overall	3	6.8	41	93.2	44
Total	Male	82	9.2	806	90.8	888
	Female	47	5.6	793	94.4	840
	Overall	129	8.1	1599	92.5	1728

a. Samples intially above the reportable range, with a result > 1.2 Index or with an initial result >0.80 Index and < 1.2 Index followed by two repeat results where 2 of the 3 results are ≥ 1.0 Index.

b. Samples initially below the reportable range, with a result < 0.80 Index, or with an initial result >0.80 Index and < 1.2 Index followed by two repeat results where 2 of the 3 results are ≤1.0 Index

c. Percents are for the numbers of reactives, equivocals, and nonreactives in a given row. If the

total number of samples in the row is zero, – is entered.

Sample Classification

The HBV disease classification for each patient considered to be high risk for HBV infection, presenting with signs and symptoms of HBV infection, or undergoing dialysis treatment (a total of 1678 patients) 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 6 HBV markers: HBsAg, HBeAg, anti-HBc Total, anti-HBc IgM, anti-HBe, and anti-HBs. A testing of these specimens occurred at external and internal study sites.

A retrospective study included 50 samples from HBV chronically infected patients from Vietnam. These samples were obtained from the commercial vendor. Vendor assignment of HBV chronic samples was based upon positive HBsAg results after six months of HBV infection. Vendor assignment was verified by HBV marker testing at the clinical sites. These samples were tested with both the ADVIA Centaur HBeAg assay and a reference HBeAg assay at the clinical trial sites.

Samples collected in 2002 were tested with Abbott assays for aHBs, HBsAg, HBcM and HBcT. The DiaSorin assays were used for aHBe and HBeAg. Samples that were collected in 2005 were tested with Siemens ADVIA Centaur assays for aHBs, HBsAg, HBcM and HBcT. Again, the DiaSorin assays were used for aHBe and HBeAg.

Each patient's HBV infection was classified based on the reactive (+)/nonreactive (–) patterns of 6 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 26 unique reference marker patterns observed. These patterns are presented in the Table below. The data included in the Classification Table of the Performance Characterics Section of the Instructions for Use (IFU) were taken from this table.

Classification by Reference Markers (All Testing Sites)

HBV Reference Markers						
HBV Classification	**HBsAg**	**HBeAg**	**HBc IgM**	**HBc Total**	**Anti-HBe**	**Anti-HBs**
Chronic	+	+	+	+	–	+
Chronic	+	+	–	+	+	–
Chronic	+	+	–	+	–	+
Chronic	+	+	–	+	–	–
Chronic	+	–	–	+	+	+
Chronic	+	–	–	+	+	–
Chronic	+	–	–	+	–	+
Chronic	+	–	–	+	–	–
Early Recovery	–	–	+	+	+	+
Early Recovery	–	–	+	+	+	–
Early Recovery	–	–	+	+	–	–
Early Recovery	–	–	–	+	+	–
HBV Vaccine Response	–	–	–	–	–	+
Not previously infected	–	–	–	–	–	–
Recovered	–	–	–	+	–	+
Recovered	–	–	–	+	–	–
Recovery	–	–	–	+	+	+
Recovery	–	–	–	–	+	+
Uninterpretable	+	–	–	–	–	–
Uninterpretable	–	–	+	–	–	–
Uninterpretable	–	–	–	–	+	–
Uninterpretable	–	+	–	+	+	+
Uninterpretable	–	+	–	+	–	+
Uninterpretable	–	+	–	+	–	–
Uninterpretable	–	+	–	–	–	–
Unknown	+	–	–	–	+	+

* + = Reactive
* – = Nonreactive

NOTE: When the result was equivocal or indeterminate, it was assumed to be nonreactive (-) for classification purposes.

Results by Specimens

A total of 1678 patients 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 6 HBV markers: hepatitis B virus surface antigen (HBsAg), hepatitis B virus e antigen (HBeAg), total antibody to hepatitis B virus core antigen (anti-HBc Total), IgM antibody to hepatitis B core antigen (anti-HBc IgM), total antibody to HBeAg (anti-HBe), and total antibody to hepatitis B virus surface antigen (anti-HBs) (quantitative). 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.

Comparison of Results by Risk Groups for Hepatitis: ADVIA Centaur HBeAg Assay versus HBeAg Reference Assay (All Testing Sites)

	Reference HBeAg Nonreactive		**Reference HBeAg Reactive**		**Reference HBeAg Equivocal**		
	ADVIA Centaur HBeAg Assay		**ADVIA Centaur HBeAg Assay**		**ADVIA Centaur HBeAg Assay**		
Risk Group	Reactive	Nonreactive	Reactive	Nonreactive	Reactive	Nonreactive	**Total**
	N	N	N	N	N	N	N
Signs and Symptoms	19	583	42	3	0	0	647
High Risk[a]	11	901	12	2	0	0	926
Dialysis	2	102	0	1	0	0	105
Total	32	1586	54	6	0	0	1678

[a] The High Risk Group includes the following subgroups: hepatitis history, hemophiliac, intravenous drug-user, transplant and/or transfusion, high-risk sex, healthcare worker, HIV-infected, other unspecified.

Prospective Population: Following the assignment of specimen classification, the HBV results obtained using the ADVIA Centaur HBeAg assay were compared with results obtained using the reference HBeAg assay for each result category (i.e. reactive and nonreactive). Specimens with an HBeAg value within the retest zone were retested and interpreted as described under *Interpretation of Results*. A total of 1678 prospective samples were run using the ADVIA Centaur HBeAg assay and a reference HBeAg assay for each HBV specimen classification. The method comparison for all testing sites combined is presented in the following table:

Comparison of Prospective Results by HBV Classification: ADVIA Centaur HBeAg Assay versus HBeAg Reference Assay (All Testing Sites)

	Reference HBeAg Nonreactive		Reference HBeAg Reactive		
	ADVIA Centaur HBeAg Assay		ADVIA Centaur HBeAg Assay		
	Reactive	Nonreactive	Reactive	Nonreactive	Total[a]
HBV Classification	N	N	N	N	N
Chronic	6	57	52	0	115
Early Recovery	1	58	0	1	60
Recovery	6	141	0	0	147
Recovered	8	153	0	0	161
HBV Vaccine Response	13	352	0	2	367
Not previously infected	25	789	0	0	814
Uninterpretable	0	8	2	3	13
Unknown	0	1	0	0	1
Total	59	1559	54	6	1678

[a]Total numbers of categories

Prospective Population

The agreement between the ADVIA Centaur HBeAg assay and a reference HBeAg assay for each HBV specimen classification is listed in the table below. The reference assay has an equivalent zone, but the ADVIA Centaur assay does not. Therefore, the single sample equivocal on the reference assay is excluded from the agreement calculations (it was reactive on the ADVIA Centaur system).

Percent Agreement and Confidence Intervals by HBV Classification Populations: ADVIA Centaur HBeAg Assay versus HBeAg Reference Assay (All Testing Sites)

HBV Classification	Positive Agreement		Negative Agreement	
	% (x/n)[a]	95% Confidence Interval	% (x/n)[b]	95% Confidence Interval
Chronic	100.0 (52/52)	93.2-100.0	90.5 (57/63)	80.4-96.4
Early Recovery	0.0 (0/1)	0.0-97.5	98.3 (58/59)	90.9-100.0
Recovery	- (0/0)	-	95.9 (141/147)	91.3-98.5
Recovered	- (0/0)	-	95.0 (153/161)	90.4-97.8
HBV Vaccine Response	0.0 (0/2)	0.0-84.2	96.4 (352/365)	94.0-98.1
Not previously infected	- (0/0)	-	96.9 (789/814)	95.5-98.0
Uninterpretable	40.0 (2/5)	5.3-85.3	100.0 (8/8)	63.1-100.0
Unknown	- (0/0)	-	100.0 (1/1)	2.5-100.0
Total	90.0 (54/60)	79.5-96.2	96.4 (1559/1618)	95.3-97.2

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

Retrospective Population

A population of commercially sourced HBV 50 chronic samples were also tested using both the ADVIA Centaur HBeAg Asssay and a reference HBeAg Assay in single replicates. The following results were obtained.

Comparison of Retrospective Results by HBV Chronic classification: ADVIA Centaur HBeAg Assay versus HBeAg Reference Assay (All Testing Sites)

	Reference HBeAg Nonreactive		Reference HBeAg Reactive		
	ADVIA Centaur HBeAg Assay		ADVIA Centaur HBeAg Assay		
	Reactive	Nonreactive	Reactive	Nonreactive	Total
HBV Classification	N	N	N	N	N
Chronic	0	35	15	0	50

Prospective Percent Agreement

The agreement between the ADVIA Centaur HBeAg Assay and a reference HBeAg Assay for the own and the way you are you 111 the chronic HBV specimen classification is listed in the following table:

Percent Agreement and Confidence Intervals by HBV Chronic Classification Populations: ADVIA Centaur HBeAg Assay versus HBeAg Reference Assay (All Testing Sites)

	Positive Agreement		Negative Agreement	
HBV Classification	% (x/n)[a]	95% Confidence Interval	% (x/n)[b]	95% Confidence Interval
Chronic	100.0 (15/15)	78.2-100.0	100.0(35/35)	90.0-100.0

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

Seroconversion Panels

To evaluate the clinical sensitivity of the ADVIA Centaur HBeAg Assay in the detection of HBeAg, commercially available hepatitis B seroconversion panels were tested, in parallel, with the ADVIA Centaur HBeAg Assay and the DiaSorin, Inc., ETI-EBK PLUS enzyme immunoassay (FDA approved comparator HBeAg Assay) for the qualitative detection of HBeAg.

Seroconversion Panels studies were performed at two different times. First studies included two commercially panels RP009 and RP016 tested at two sites. Second studies included the additional data from the testing of 5 more serocoversion panels (11015, 11024, 6278, 11004, PHM935B). The seroconversion testing results

showed that the ADVIA Centaur HBeAg Assay was equally sensitive to the Diasorin HBeAg Assay. Results are summarized in the table below.

	HBeAg Reactive Result From Initial Draw Date		**Reference Assay vs ADVIA Centaur Assay**
Panel ID	Reference Assay (Days)	ADVIA Centaur Assay (Days)	Difference in bleed number[a]
RP-009	11	11	0
RP-016	56	56	0
11015	71	71	0
11024	50	50	0
6278	17	17	0
11004	49	49	0

[a]The difference in bleed numbers is relative to the reference assay.
Note: One panel (PHM935B) was positive for HBeAg on first bleed date tested by both the Centaur and reference.

Reproducibility

The ADVIA Centaur HBeAg Assay reproducibility study was performed at 2 external sites and at Siemens in Tarrytown utilizing 3 reagent lots per site. A 5-member panel, controls and calibrators (run as unknowns) were assayed in replicates of 4 with 2 runs per day for 5 days for each lot at each site. Two external and one internal clinical sites participated in the study.

The study was completed with a single calibration of the assay (one calibration interval) for each lot and site. The data from all 3 sites were combined for each lot to estimate SD and percent CV within run, between run, and within testing site precision components pooled across sites, and to estimate the between testing site and total (within lot) precision components. The analysis of data was based on guidance from the CLSI documents EP5-A2 and EP15-A2. Standard deviation and percent coefficient of variation (CV) were calculated for within run, between run, between testing site between lot and total precision components. Results are summarized below:

Reproducibility

Panel Members	Mean Index Value	Within-Run		Between-Run		Among Site		Among-Lot		Total		Number of Observations
		SD	CV %	SD	CV %	SD	CV (%)	SD	CV (%)	SD	CV (%)	
1	0.47	0.18	39.1	0.02	4.5	0.04	9.3	0.15	31.7	0.25	52.1	354*
2	1.10	0.15	13.5	0.06	5.1	0.04	3.2	0.08	7.4	0.19	17.1	360
3	1.89	0.20	10.5	0.06	3.2	0.09	4.8	0.02	1.2	0.23	12.2	360
4	28.30	1.10	3.9	0.32	1.1	1.21	4.3	2.02	7.1	2.65	9.4	360
5	216.98	7.74	3.6	2.17	1.0	9.72	4.5	19.52	9.0	23.38	10.8	360

*Six replicates were below the range of the assay.

Alternative Sample Types

The ADVIA Centaur HBeAg Assay can use plasma specimens collected using either potassium EDTA, sodium heparin, or lithium heparin anticoagulants. Fifty negative samples were collected in various tube types. Fifteen sets were spiked to obtain Index values between 1 and 10. Fifteen specimens were spiked to obtain Index values between 10 and 50 Index. Twenty sets remained negative (below Index 1.0). The percent difference between the serum Index value and the matched plasma Index value was calculated for each sample pair. The number of samples within a range of percent differences was then tabulated. The table below provides the number of positive sample pairs within each percent difference range. The percent differences were not tabulated for the negative samples because the values for the negative samples ranged from below the lower end of the assay range to 0.38 Index. For each sample set, the clinical interpretation remained that same in all tube types. Results are summarized below.

Distribution of % Difference to Serum	Collection Tube Type		
	Potassium EDTA	Lithium Heparin	Sodium Heparin
>-20%	0	0	0
-20 to -10%	16 % (5/30)	13.3% (4/50	13.3% (4/50
-10 to -5%	26.6% (8/50)	33.3% (10/30)	33.3% (10/30)
-5 to 0%	33.3% (10/30)	(26.6% (8/30)	30% (9/30)
0 to 5%	16 % (5/30)	13.3% (4/30)	13.3% (4/30)
5 to 10%	(6.6% (2/30)	3.3% (1/30)	(6.6% (2/30)
10 to 20%	0	(6.6% (2/30)	3.3% (1/30)
>20%	0	3.3% (1/30)	0

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 studies conducted to support PMA approval as described above. As a diagnostic test, the ADVIA Centaur HBeAg Assay involves removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood is removed.

False positive and false negative results are discussed in Section VIII - Potential Adverse Effects of the Device on Health. There were no adverse effects of the device reported while the study was conducted.

B. Effectiveness Conclusions

Multicenter clinical studies were conducted in the US. ADVIA Centaur HBeAg Assay when used on ADVIA Centaur and ADVIA Centaur XP systems performed with clinical sensitivity and specificity comparable to current commercially available FDA approved HBeAg assay.

- The ADVIA Centaur Hepatitis HBeAg Assay performance is acceptable when testing in serum, gel separator tubes and lithium heparin, K_2-EDTA and sodium citrate plasma in glass and plastic.

- Samples are stable when refrigerated for 7 days (2-8°C) or frozen for 1 year (-20°C). They can also withstand 3 freeze/thaw cycles.

- The ADVIA Centaur HBeAg reagents, calibrators, and controls demonstrate stability of 24 months when stored at 2-8°C. It is stable on-board the on-board the ADVIA Centaur and ADVIA Centaur XP systems for 60 days.

- The ADVIA Centaur HBeAg Assay calibrators and controls are stable on-board the ADVIA Centaur and ADVIA Centaur XP systems for 8 hours. The calibrators are stable for 8 weeks when stored at 2-8°C.

- The comparison of the performance of ADVIA Centaur HBeAg Assay to the FDA approved comparator HBeAg test in subjects with serologically determined chronic HBV infection resulted in a positive percent agreement of 100.00% (52/52) with a 95% confidence interval from 93.2% to100.0%. The negative percent agreement with the FDA approved comparator HBeAg test for this group was 90.5% (57/63) with a 95% confidence interval from 80.4% to 96.4%

- Seroconversion sensitivity of the ADVIA Centaur HBeAg Assay has been shown to be acceptable by testing 7 commercial seroconversion panels in comparison to a FDA approved comparator HBeAg assay.

- Analytical specificity studies evaluated the potential cross reactivity in specimens from potentially cross-reacting clinical subgroups. It has been shown that the device has no significant cross-reactivity with these potentially cross-reacting clinical subgroups, and other viral pathogens that may cause similar symptoms or are closely related to HBV.

- There are no issues with endogenous interferents at physiological levels, or with the effect of potential interferents (bacterial and recombinant viral antigens) on the performance of the ADVIA Centaur HBeAg Assay.

- The ADVIA Centaur HBeAg Assay demonstrated an acceptable total variability (incorporating factors of site, lot and day) of 5.9 to 10.6%. The individual precision estimates for the different components of variance were: <13.5% for within day, <5.1% between day, < 9% between lot, < 4.8% between site.

The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur HBeAg Assay is effective for the *in vitro* qualitative detection of HBeAg in human serum and plasma. The ADVIA Centaur HBeAg Assay results, in conjunction with other serological and clinical information, may be used for the laboratory diagnosis of individuals with chronic hepatitis B, or recovery/recovered from hepatitis B infection.

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 HBeAg Assay, when compared to FDA approved comparator, has a similar

compared to the assay. It has been shown that the device has no demonstrable cross-reactivity with viruses or organisms that may cause clinical hepatitis. Therefore, this device should benefit the physician to aid in the laboratory diagnosis of individuals with chronic hepatitis B, or recovery/recovered from hepatitis B infection.

XIII. CDRH DECISION

FDA issued an approval order on October 11, 2011. The final conditions of approval are cited in the approvable order.

The applicant's manufacturing facilities were inspected and found to be in compliance with the devices 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.