SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I.   ## GENERAL INFORMATION

Device Generic Name:	ADVIA Centaur HBc IgM assay
Device Trade Name:	ADVIA Centaur® HBc IgM ReadyPack Reagents ADVIA Centaur® HBc IgM 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:	P030040

Date of Notice of Approval to Applicant: August 6, 2004

II. ## INDICATIONS FOR USE

ADVIA Centaur® HBc IgM ReadyPack Reagents:

The ADVIA Centaur HBc IgM assay is an *in vitro* diagnostic test for the qualitative determination of IgM response to hepatitis B virus core antigen in human serum and plasma (EDTA or lithium or sodium heparinized) using the ADVIA Centaur® System. The assay uses recombinant HBc antigen. This assay may be used in combination with other hepatitis B virus (HBV) marker assays to define the clinical status of known HBV infected patients or can be combined with other HBV, HAV (hepatitis A virus), and HCV (hepatitis C virus) assays for the diagnosis of patients presenting symptoms of acute viral hepatitis.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, cord blood, neonatal specimens, infants or children.

Assay performance characteristics have not been established when the ADVIA Centaur HBc IgM assay if used in conjunction with other manufacturers' assays for specific HBV serological markers.

HBc IgM Quality Control Materials:

The controls are indicated for in vitro diagnostic use in monitoring the performance of the HBc IgM assay on the ADVIA Centaur® Systems. The performance of the HBc IgM quality control material has not been established with any other anti-HBc IgM assays.

III.   CONTRAINDICATIONS: NONE

IV.   WARNINGS AND PRECAUTIONS:

Warnings and Precautions for the ADVIA Centaur HBc IgM assays are stated in the product insert.

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

V.   DEVICE DESCRIPTION

The ADVIA Centaur® HBc IgM assay is an indirect IgM capture immunoassay using a two step format. It is designed for the qualitative detection of HBc IgM in human serum or plasma. The Assay reagent kit consists of an Ancillary Reagent containing biotinylated anti-human IgM, a Solid Phase containing streptavidin coated paramagnetic microparticles, and a Lite Reagent containing recombinant HBc antigen (rHBcAg) labeled with acridinium ester (AE).

Sample is first incubated with the Ancillary Reagent for 6 minutes at 37°C. During this incubation biotinylated anti-human IgM monoclonal antibody binds to IgM present in the sample. The Solid Phase is added next, and the streptavidin coated microparticles in the Solid Phase bind the biotin of the sample IgM / Ancillary Reagent complex during incubation. The microparticles are then held fast by a magnet and washed multiple times to remove unbound sample. Lite Reagent is next added and the reaction mix is incubated. Recombinant HBc antigen in the Lite Reagent binds to any HBc IgM present in the sample. The microparticles are then held fast by a magnet and washed multiple times to remove unbound Lite Reagent. 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 measured as relative light units (RLUs) by the photomultiplier tube (PMT) of the ADVIA Centaur Instrument. A RLU value is compared to a stored calibration curve to generate a patient result.

Use of HBc IgM alone is not recommended but should be utilized in conjunction with other HBV markers for a more complete evaluation of the patient's status.

The ADVIA Centaur® HBc IgM assay utilizes a factory preset Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The master curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values on the system. The two calibrators in the kit are run when the lot is first used or after expiration of the calibration interval (28 days). If the calibration run is valid as determined by pre-set parameters, the values are stored and used to "normalize" test values to the Master Curve. The system reports HBc IgM results in Index Value sand as reactive, equivocal, or nonreactive. Samples with a calculated value greater than or equal to 1.00 Index Value are considered reactive for IgM antibodies to hepatitis B core antigen.

VI.   ALTERNATIVE PRACTICES OR PROCEDURES

Determination of the presence of anti-HBc IgM 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 biochemical test results, a diagnosis of infection with HBV can be established.

VII.   MARKETING HISTORY

The ADVIA Centaur® HBc IgM assay is currently being marketed internationally in

accordance with Section 802 of the FD&C act. This product has not been withdrawn from any country for any reason.

The countries where this device is currently being marketed are:
The Americas: Canada, Colombia
Europe: Nordic (Sweden, Norway, Finland), France, Germany, Italy, Spain, Portugal, UK, Benelux, Poland
and other Eastern European countries, Austria, Greece, Switzerland
Africa: South Africa
Asia: Japan, Australia, New Zealand, Singapore, Korea, Malaysia, India

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There are no known potential direct adverse effects of this device on the health of the user if the device is used according to the instructions in the package insert. However, failure of the test to perform as indicated or human error during performance of the test may lead to a false diagnosis and improper patient management.

A false-positive result using ADVIA Centaur® HBc IgM assay is not considered a patient or public health concern since a reactive EIA result in a clinical lab should be interpreted in conjunction with other hepatitis assay markers and signs and symptoms of the disease.

A single false negative anti-HBc IgM result in a diagnostic setting may lead to a patient with hepatitis going unidentified unless the patient is tested with other HBV marker assays to define his/her clinical status. If multiple marker testing is not performed, there is concern for both the patient and the public
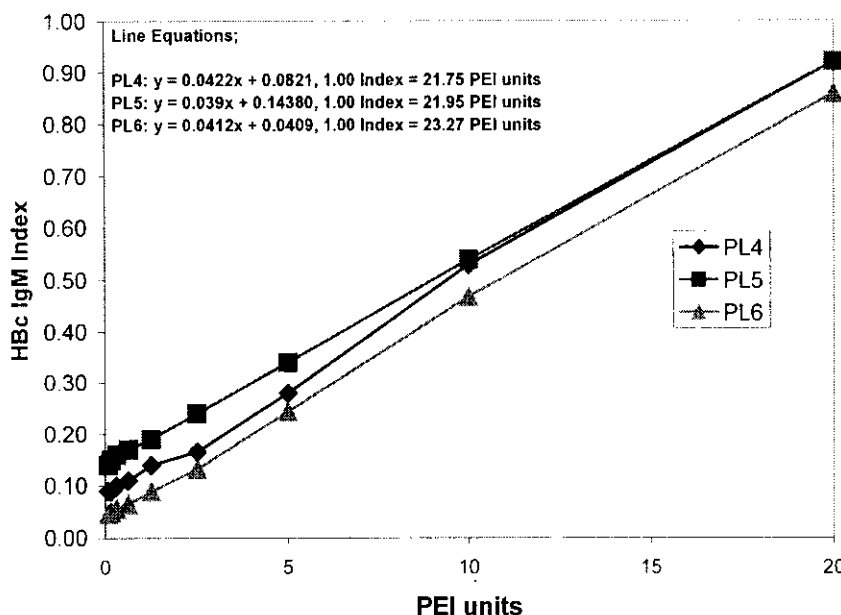
IX. SUMMARY OF PRECLINICAL STUDIES

The applicant performed in-house studies in order to evaluate the following performance characteristics of the ADVIA Centaur® HBc IgM: cutoff determination and verification, sample handling and collection, interference, sample carryover and stability. In addition, testing was performed with performance panels, seroconversion panels, and a panel of potentially cross-reacting samples. Cross-reactivity testing, specificity testing (by removing IgM with a reducing agent), specimen matrix effect testing, and environmental testing were also performed. .

Laboratory Studies

In order to evaluate the analytical sensitivity of this device, the sponsor determined the concentration of the Paul Ehrlich Institute (PEI) anti-HBc IgM reference unit that corresponds to the cutoff value (Index Value of 1.00) of the ADVIA Centaur® HBc IgM assay. A dilution series was prepared in a negative plasma based-pool by making an initial 1:5 dilution of the PEI reference material and serially diluting to a final dilution of 1:1280. This dilution series was tested using three pilot lots of HBc IgM reagents. The results are presented in the following figure.

ADVIA Centaur HBc IgM; Dilution of PEI unit
Pilots 4,5, & 6 (2pt curves)

Line Equations;

PL4: y = 0.0422x + 0.0821, 1.00 Index = 21.75 PEI units
PL5: y = 0.039x + 0.14380, 1.00 Index = 21.95 PEI units
PL6: y = 0.0412x + 0.0409, 1.00 Index = 23.27 PEI units

HBc IgM Index (y-axis: 0.00 to 1.00)
PEI units (x-axis: 0 to 20)

Legend: PL4, PL5, PL6

When the response curves were extrapolated to the cutoff value (Index Value Value of 1.00) the estimates of PEI concentration at the cutoff value were 21.75 to 23.27 (mean = 22.32, 95% Confidence Interval = 20.70 – 23.94).
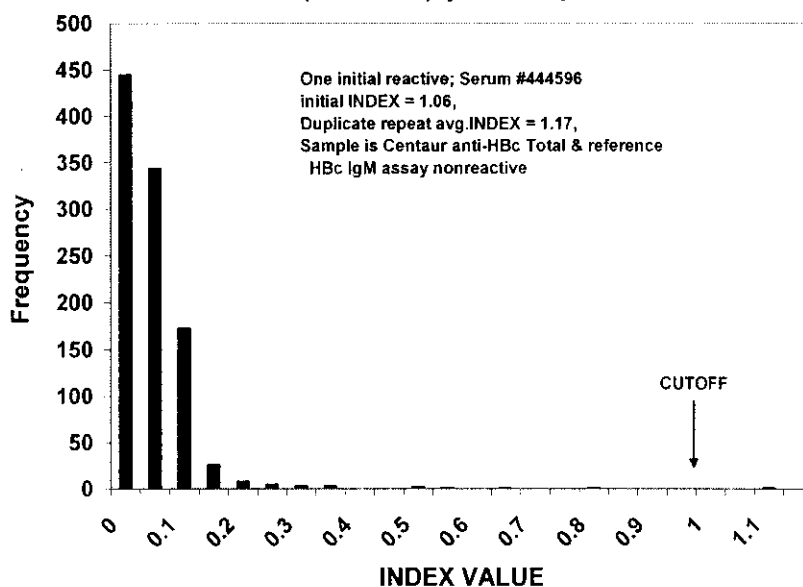
HBV performance panels

A set of commercially available performance panels comprised of HBc IgM positive serum and plasma samples in a range of titers were tested with ADVIA Centaur® HBc IgM reagents. To determine agreement with known positive specimens, three performance panels were evaluated; HBc IgM low-titer (n=15), HBc IgM mixed-titer (n=25), and HBc total mixed-titer (n=25). Combining results from the 3 panels, demonstrated agreement with Reference HBc IgM assays for 63 of 65 samples. The remaining two samples were reactive by some reference assays and nonreactive using others. These results demonstrate that the sensitivity of the ADVIA Centaur HBc IgM assay is equivalent to commercially available HBc IgM assays.

Volunteer Donor Population

Serum and plasma specimens from a population of volunteer blood donors were tested to establish the nonreactive distribution and specificity of the ADVIA Centaur® HBc IgM assay. A total of 1013 fresh/unfrozen samples were tested using ADVIA Centaur® HBc IgM. The following figure is a histogram of the volunteer donor population Index Values. One sample was above the cutoff value (see table within figure). This sample is Centaur® HBc total nonreactive and reference HBc IgM assay nonreactive. The calculated specificity for this population is 1012/1013 = 99.90%. These results demonstrate that the specificity of ADVIA Centaur HBc IgM assay is acceptable.

Fresh normal donors N = 1013 (432 serum, 321 EDTA plasma, 260 Heparin (Na & Li) plasma)

One initial reactive; Serum #444596
initial INDEX = 1.06,
Duplicate repeat avg.INDEX = 1.17,
Sample is Centaur anti-HBc Total & reference
HBc IgM assay nonreactive

CUTOFF

Frequency

INDEX VALUE

HBV Seroconversion Panels

Four HBV patient seroconversion panels were tested with the ADVIA Centaur® HBc IgM assay to demonstrate how soon this assay becomes reactive compared to a reference assay. Samples in the four panels selected represent the patients' HBV seroconversion through early infection, acute phase, and recovery. The ADVIA Centaur® HBc IgM assay results were compared to the results from commercially available HBc IgM assays. For the four panels, the ADVIA Centaur® HBc IgM assay becomes reactive at the same time or slightly earlier than the Reference assay and returns to nonreactive or low reactive at approximately the same time as the Reference assay. These results demonstrate that the sensitivity of the ADVIA Centaur HBc IgM assay is equivalent to commercially available HBc IgM assays. Additional seroconversion panel study data generated during U.S. clinical trials are presented in the "Summary of Clinical Studies" section of this document.

Potential Cross Reactive Specimens

A study was performed to evaluate the ADVIA Centaur® HBc IgM assay for potential cross-reactivity to other disease states, viruses, microorganisms, or historically problematic specimens. One hundred sixty four distinct serum and plasma specimens from 18 groups of potential cross-reactants were assayed. The vendor used FDA-approved/510(k) cleared devices to confirm the disease state of each specimen. The ADVIA Centaur® HBc IgM testing was done in a single determination. One sample in the rheumatoid factor (RF) group was ADVIA Centaur® reactive and reference HBc IgM assay nonreactive. One sample in the Rubeola IgG group was ADVIA Centaur® reactive and reference HBc IgM assay equivocal. This sample was also ADVIA Centaur® HBc Total reactive. A second sample in the Rubeola IgG group was ADVIA Centaur® equivocal and Reference HBc IgM assay elevated nonreactive. Results of the cross-reactivity study are presented in the following table.

ADVIA	Centaur	HBc IgM Results		
Clinical Category	Number Tested	Nonreactive	Equivocal	Reactive
Hepatitis A Infection (HAV)	9	9	0	0
Hepatitis C Infection (HCV)	12	12	0	0
Epstein-Barr Virus (EBV) IgM	10	10	0	0
Herpes Simplex Virus (HSV) IgG	10	10	0	0
Herpes Simplex Virus (HSV) IgM	10	10	0	0
Parvovirus IgM	5	5	0	0
Syphilis IgG	10	10	0	0
Syphilis IgM	10	10	0	0
Human Immunodeficiency Virus (HIV1/2)	10	10	0	0
VZV IgG	9	9	0	0
VZV IgM	6	6	0	0
Rubeola IgG	11	9	1[1]	1[2]
Non-viral Liver Disease	12	12	0	0
Rheumatoid Arthritis	12	11	0	1[3]
Anti-Nuclear Antibody (ANA)	6	6	0	0
Systemic Lupus Erythematosus (SLE)	3	3	0	0
Flu Vaccine Recipient	10	10	0	0
HAMA	9	9	0	0
Total Samples Tested	164	161	1	2

1. Sample had a 0.95 Index Value using the ADVIA Centaur HBc IgM assay and a 0.63 Index Value (Elevated Negative) using the reference HBc IgM assay.

2. Sample had a 1.39 Index Value using the ADVIA Centaur HBc IgM assay and a 0.86 Index Value (Equivocal) using the reference HBc IgM assay.

3. Sample had a 1.24 Index Value using the ADVIA Centaur HBc IgM assay and a 0.25 Index Value (Negative) using the reference HBc IgM assay.

Note: Because the recombinant antigen was produced in yeast and because cross-reactivity testing was not performed with this vector, the user should be made aware of this fact. Therefore, a statement to this effect is placed in the Limitations section of the product insert.

Endogenous Interferants

The ADVIA Centaur® HBc IgM assay was tested to evaluate for interference following the guidelines described in the approved standard, NCCLS EP07-A, for interference due to high levels of endogenous substances. The effects of conjugated bilirubin @ 60 mg/dL, unconjugated bilirubin @ 40 mg/dL, hemoglobin @ 500 mg/dL, triglycerides @ 1000 mg/dL, and human serum albumin @ 12 g/dL (ie, high total protein) were evaluated in serum and plasma samples. Fifteen patient samples ranging from nonreactive to high reactive were used. Average % recovery of spiked vs. unspiked treatments ranged from 98.8 to 100.5. No interference was found.

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Interfering Substance-HBc IgG

A study was performed to demonstrate that HBc specific IgG in samples does not interfere with the ability of the ADVIA Centaur® HBc IgM assay to detect HBc specific IgM. Blood was drawn from 17 in-house, healthy donors into serum, EDTA and heparin plasma tubes, then spiked with a high positive HBc IgM pool to create specimens reactive at Index Value levels across the assay dynamic range. Each sample was then spiked with high titer HBc IgG. There was no significant shift in Index Value resulting from spiking with the HBc IgG. The mean percentage recovery (IgM+/IgG+ Index Value vs. IgM+/IgG- Index Value) was within 5% of 100 for each matrix, indicating no interference from HBc IgG.

Dithiothreitol (DTT) Treatment of HBc IgM Reactive Specimens

Further support that the ADVIA Centaur® HBc IgM assay is specific for IgM antibody was demonstrated by testing HBc IgM reactive specimens that had been treated with the reducing agent, DTT. Incubation with the reducing agent causes the IgM within the samples to break apart, making it impossible for the ADVIA Centaur® HBc IgM assay format to detect IgM. Samples were drawn from healthy in-house donors and spiked with high positive HBc IgM plasma. An aliquot was removed from each spiked sample and incubated with 5 mM DTT at 37C for 1 hour. Reduced and control aliquots were run together on the ADVIA Centaur® and percent reduction of the DTT treated sample Index Value versus the untreated sample Index Value was calculated. Of the 15 reactive and 1 equivocal specimens tested, all became nonreactive when reduced by DTT treatment. This study indicates that the HBc IgM assay is specific for IgM class antibody.

Sample	Neat Index Value	5mM DTT Treatment Index Value	% Reduction of Index Value
P1	2.34	0.02	99.1%
P2	1.13	0.02	98.6%
P3	7.93	0.12	98.5%
P4	3.57	0.05	98.6%
P5	1.57	0.02	98.8%
P6	0.96	0.02	98.1%
P7	1.57	0.02	98.7%
P8	1.87	0.02	98.8%
P9	2.21	0.02	98.9%
P10	5.23	0.15	97.2%
P11	1.58	0.24	84.6%
P12	1.44	0.04	97.3%
P13	1.32	0.09	93.5%
P14	2.35	0.30	87.1%
P15	1.66	0.44	73.3%
P16	14.43	0.56	96.2%

Precision Studies

To demonstrate the precision of this assay, a single instrument and recommendations from the approved standard, NCCLS EP5-A, were utilized in a precision study using ADVIA Centaur® HBc IgM Reagents. The study was set up as both an evaluation of the HBc IgM assay precision versus imprecision goals and as a study of the effect of sample matrix (serum versus five plasma anti-coagulants) on specimen precision. For each anti-coagulant, a single donor unit was used to prepare a five-member panel targeting the following HBc IgM ranges (high HBc IgM positive serum was used to prepare spiked reactive panel members):

1. 0.0-0.3 Index Value (nonreactive, un-spiked)

2. 0.6-0.9 Index Value (elevated nonreactive/equivocal, spiked)

3. 1.0-2.0 Index Value (low reactive #1, spiked)

4. 2.0-3.0 Index Value (low reactive #2, spiked)

5. 5.0-7.0 Index Value (high reactive, spiked).

The ADVIA Centaur® HBc IgM Ready-packs were taken from 4°C storage and placed on the ADVIA Centaur® as needed. 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 Value values of standards, controls, calibrators, serum pools, QC panel members, and spiked HBc IgM specimen panels prepared in serum and three plasma types were calculated using a stored curve established by two-point calibrator adjustment of the reagent master curve using day one, run one Low and High calibrators. Specimen panel within run percent CVs ranged from 0.8% to 7.6%. Specimen panel total percent CVs range from 1.0% to 8.6%. Additional Precision study data generated during U.S. clinical trials are presented in the "Summary of Clinical Studies" section of this document. This laboratory precision study demonstrated that the Advia Centaur® HBc IgM assay has acceptable precision.

Matrix, Collection Tube Type, Effects

Blood was collected during in-house blood draws from 52 healthy, normal donors in Red Top (serum), SST (serum), K2 EDTA (plasma), Na Heparin (plasma), and Li Heparin (plasma) to determine if there were any difference in results when using serum or plasma. Forty-nine of these samples were tested on the ADVIA Centaur® to simulate a nonreactive donor population, then spiked with high titer HBc IgM positive pool plasma to form a reactive population that was also tested on the Centaur. Spiking volume was varied among samples to represent a reactive population in which the full assay dynamic range was represented. Samples 50, 51, and 52 were only run as spiked reactive specimens. The results demonstrate that, for these anti-coagulants, specimen Index Value does not vary as a function of collection tube type. The spiked samples had reactive sample Index Values for SST serum (gel barrier), K2 EDTA plasma, Li Heparin plasma, and Na Heparin plasma were within 5% of the serum Red Top Index Value when averaged across the 52 samples. These anticoagulant and collection tube types can all be used for collection of specimens to be assayed using the ADVIA Centaur® HBc IgM assay. Some individual heparin Index Value values were up to 28% greater than the serum sample control.

Sample Handling Studies

The sponsor conducted sampling handling studies to determine if test results were affected when specimens were subjected to potential stresses such as freeze/thaw or elevated temperature storage. When specimens were tested in comparison to baseline data to determine the impact of the stress on assay accuracy, the sample handling studies described here evaluated the effect of the following patient sample handling conditions on ADVIA

Centaur® HBc IgM Index Value:

1. Extended time on-board the ADVIA Centaur® Instrument (simulated by non-capped storage @ 30°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. 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® HBc IgM assay on the day of collection. All percentage recoveries are calculated against the baseline (day 0) value. Results from the ADVIA Centaur® HBc IgM sample handling studies support the claims that samples can be subjected to the following conditions and still generate accurate results when tested in ADVIA Centaur® HBc IgM assay:

1. Samples can be kept on-board the ADVIA Centaur® instrument for up to 8 hours.

2. Samples can be stored at room temperature for up to 2 days.

3. Samples can be stored refrigerated (2-8°C) for up to 3 days.

4. Samples can be stored frozen (-20°C) for long term storage.

5. Samples can be frozen and thawed up to four times.

<u>On-The-Clot Specimen Storage</u>

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 a secondary container will affect the HBc IgM Index Value. Fresh samples were drawn from 15 healthy in-house donors into serum and plasma collection tube types to be tested. The specimens were centrifuged within the recommended time and an aliquot from each primary tube was placed in another container (HBc IgM positive specimens were carefully spiked with high positive HBc IgM plasma before removing the aliquot). The primary (collection) tube and the removed aliquot were then stored at 4°C and tested side by side in the ADVIA Centaur® HBc IgM assay at 1, 3, and 7 days after collection. There is no evidence of any effect on assay result due to a sample being left in the primary collection tube for up to seven days in 4°C storage.

<u>Sample Processing – Time to Centrifugation</u>

A study was done to determine the effect of fresh sample holding time to centrifugation on the HBc IgM Index Value. Three studies of five donors each were performed. For all studies three fresh samples were drawn from healthy in-house donors in serum and plasma collection tubes. The tubes were spiked with HBc IgM positive pool and centrifuged shortly after collection, after six hours or after 24 hours. Aliquots from the three 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 Index Value to shift. Percentage Recovery Grand Mean of all reactive specimens in all tube types was 96.3% for six hours and 97.1% for 24 hours. The average for each tube (matrix) type was within 10% of baseline for both six hour and 24 hour time points. Although there are some individual reactive sample Index Value recoveries that were not within +/- 10% of baseline, overall there is no evidence of any significant bias on sample Index Value from waiting up to 24 hours to centrifuge

primary collection tubes.

Sample Handling – Inversion of Gel barrier Collection tubes

A study was done to determine if inversion of gel barrier blood collection tubes interferes with ADVIA Centaur® HBc IgM assay results. Blood was drawn from 10 healthy in-house donors using serum and plasma (Li heparin) gel barrier (separator) collection tubes. Seven sample tubes were spiked with HBc IgM at different levels, the remaining three were left nonreactive. The tubes were rocked, centrifuged, and an aliquot was taken. The tubes were then inverted five times and a second aliquot was taken. The two aliquots were compared to determine if inversion altered sample Index Value. Inversion of the barrier gel collection tube, five times, had no effect on the assay results for both reactive and nonreactive samples. One sample in the SST tube slightly over-recovered (112.6%), but all other post-inversion samples read within +/- 10% of the control. The average percentage recovery was 101.02% for PST and 99.84% for SST.

Stability Studies

Real Time Stability Studies for ADVIA Centaur® ReadyPack reagents, calibrators, and controls were conducted to demonstrate the integrity of the shelf life for these reagents. Three lots of HBc IgM reagents were placed on real time stability studies. All reagents were stored at the recommended storage temperature of 2-8°C. Reagents were monitored at several checkpoints post-manufacturing date. These studies support a claim of a 79-week expiration dating at 2-8°C for the HBc IgM reagents.

Reagent On-Board Stability (OBS) Studies: Three lots of reagents were evaluated in reagent OBS studies on four ADVIA Centaur® instruments. On-Board Stability testing on the instruments occurred at several checkpoints after the reagent was placed on-board. A fresh pack served as the control for each time-point. Dose recovery within 10% or 2SD of the fresh pack served to define acceptable performance. A calibration interval of 28 days was also evaluated using these results. The on-board studies for the reagents support 41 days OBS for the ADVIA Centaur® HBc IgM reagents. The OBS studies also support a recalibration interval of 28 days.

Shipping Studies of the reagents found that the HBc IgM reagents could withstand 3x freeze/thaw cycles (-40°C to 4°C) without aggregation of the solid phase and acceptable performance. Studies also tested for shipment of upside-down packs. ReadyPack reagents stored upside down could tolerate up to eight weeks in this position although the recommended shipping conditions were to ship the ReadyPack reagents in an upright position, stored at 2-8°C.

Three lots of calibrators and two lots of controls were placed on 2-8°C long-term stability. All calibrators and controls were stored at the recommended storage temperature of 2-8°C. Reagents and calibrators were monitored at several checkpoints post manufacturing date. The Shelf-life studies to date support a claim of a 79 week expiration dating at 2-8°C for the HBc IgM calibrators and controls.

The calibrator and control open bottle use study examined the length of time the calibrator or control is stable once the vial is opened. Open vials were stored at the recommended storage conditions of 2-8°C. The open bottles were sampled periodically up to 62 days post initial opening. A fresh (unopened) bottle was evaluated at each time point to serve as controls. The acceptance criteria for this study was dose recovery within 10% (or 2SD) of the fresh bottle dose. The study supports an open bottle use lifetime of up to 62 days.

A calibrator and control shipping study was also performed. The HBc IgM calibrators and controls were evaluated after three freeze/thaw cycles and exhibited no adverse effects.

Microbiology Studies

The ADVIA Centaur® reagents contain Sodium Azide and other anti-microbials as preservatives to protect against adventitious contamination by microorganisms. The ADVIA Centaur® calibrators and controls also contain a preservative to protect against microbial contamination. Reagents and controls were challenged in a study conducted according to USP 23/NF 18. The preservative study results indicated complete and effective elimination of the microorganisms tested. Specific data are available in the Specimen Collection and Handling Section of the product insert.

A performance microbial challenge was performed using one lot of HBc IgM reagents, calibrators, and controls. Reagents and controls were inoculated with two pools of microbes then run on the ADVIA Centaur® instrument at time 0 (Baseline), 30 days and 60 days. Controls, Medical Decision Pools, and quality control (QC) panel all were within range when tested using inoculated reagents at all timepoints. Index Value of inoculated controls were close to those of non-inoculated controls at all time-points.

Instrument Studies

Reproducibility testing was performed with three different Centaur instruments at three different sites. The results demonstrated that the instruments performed within acceptable limits.

Environmental Testing

The purpose of environmental testing is to assess ADVIA Centaur® HBc IgM assay control recovery at the mean and extreme environmental conditions as specified. Each assay is calibrated and run on a single Centaur instrument in an environmental chamber set at temperatures above and below normal room temperature. These studies demonstrated acceptable performance of the HBc IgM assay 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 with 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® HBc IgM assay was evaluated for its potential affect on all other assays using the same reagent probes and for the affect of all the other assay reagents on the HBc IgM assay. To be considered compatible, there must be <5% difference in dose between test and control, or no statistically significant change in dose, or no more than 1SD difference in dose as appropriate for the assay and the control being tested.

There were no compatibility issues between this assay and any of the assays sharing the same reagent probe.

Conclusions Drawn from the Non Clinical Studies

The non clinical studies were conducted in the US at Bayer HealthCare's Tarrytown, NY site. The ADVIA Centaur® HBc IgM assay was evaluated to demonstrate performance claims for cross-reactivity, interference, precision, matrix type, specimen handling, and reagent stability. The results of these non-clinical studies support the performance claims. The results of the non-clinical studies will be used in conjunction with results of the clinical trial studies to support the intended use statements of the ADVIA Centaur® HBc IgM assay.

X. SUMMARY OF CLINICAL STUDIES

The objective of this clinical study was to assess the efficacy of ADVIA Centaur HBc IgM for detecting hepatitis B core IgM antibodies in human serum or plasma as presumptive evidence of an HBV infection. The following performance characteristics were studied:

Prospective Study

The HBV disease classification for each patient in the high risk, signs and symptoms, and dialysis populations (2021 patients total) was determined by serological assessment using hepatitis serological marker profiles obtained from commercially available, FDA-approved Reference assays. The serological assessment included the following six 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 virus core antigen (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. No patients were excluded from the complete study set due to incomplete Reference HBV serological results.

Each patient's HBV infection was classified based on the reactive (+)/nonreactive(-) patterns of the six HBV reference serological markers. Disease classification for each patient was based only on the HBV serological marker results, and did not appear to be affected by additional laboratory or clinical information. There were 31 unique reference marker patterns observed using the ADVIA Centaur® HBc IgM assay. These patterns are presented in the following table.

Bayer ADVIA Centaur® Anti-HBc IgM Assay Classification by HBV Reference Markers (All Testing Sites)						
HBV Reference Markers						HBV Classification
HBsAg[a]	HBeAg	IgM Anti-HBc	Total Anti-HBc	Anti-HBe	Anti-HBs (>10 mIU/mL)	
+	+	+	+	+	-	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

(a) Reactive (+) = Reference HBsAg assay result was reactive and confirmed to be reactive by neutralization
Nonreactive (-) = Reference HBsAg assay result was nonreactive, or reactive, but non-confirmed by neutralization

Note: when the result was 'EQUIVOCAL', it was assumed to be nonreactive (-)

Data Analysis and Results

Device Failures and Replacements – There were no apparent reported failures and/or replacements.

Following the assignment of specimen classification, the HBV results obtained using the ADVIA Centaur® method were compared with results obtained using the reference method for each result category (reactive, nonreactive, and equivocal). Specimens with equivocal results were retested. The method comparison for all testing sites combined is presented in the following table.

HBV	Reference Anti- HBc IgM Assay			Reference Anti- HBc IgM Assay			Reference Anti- HBc IgM Assay			
	Negative			Equivocal/Grey Zone			Positive			
	ADVIA Centaur HBc IgM Assay			ADVIA Centaur HBc IgM Assay			ADVIA Centaur HBc IgM Assay			
Classification	Reactive	Nonreactive	Equivo-cal[a]	Reactive	Nonreactive	Equivo-cal[a]	Reactive	Nonreactive	Equivo-cal[a]	Total
Acute	0	0	0	0	0	0	2	0	1	3
Chronic	4	104	0	7	3	1	0	1	0	120
Early Recovery	3	108	0	1	0	0	2	1	0	115
Recovery	1	210	0	2	0	0	0	0	0	213
Recovered	1	326	1	2	0 .	0	0	0	0	330
HBV Vaccine Response	0	384	0	0	0	0	0	0	0	384
Not previously Infected	2	833	1	0	0	0	0	0	0	836
Uninterpre--table	0	20	0	0	0	0	0	0	0	20
Total	11	1985	2	12	3	1	4	2	1	2021

a   Equivocal results following repeat testing

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

Positive percent agreement =

Number of Centaur® HBc IgM reactive results in agreement w/Reference anti-HBc IgM X 100 Total number of reference anti-HBc IgM reactive results

Negative percent agreement =

Number Centaur® HBc IgM nonreactive results in agreement w/Reference anti-HBc IgM X 100 Total number of reference anti-HBc IgM nonreactive results

Overall percent agreement =

Number of Centaur® HBc IgM results in agreement with Reference anti-HBc IgM X 100 Total number of reference anti-HBc IgM reactive and nonreactive results

Any Centaur discrepant equivocal result was given the result of the comparative device. Four ADVIA Centaur nonreactive / Reference assay reactive discrepants and fourteen ADVIA Centaur reactive / Reference assay nonreactive discrepants resulted from the assignment of opposite interpretations to equivocal samples. The one sample which was equivocal in both assays was considered a negative concordant sample for the purpose of calculating % agreement. The following results were obtained:

HBV Classification	% Positive Agreement	95% Exact Confidence Interval (CI)	% Negative Agreement	95% Exact Confidence Interval (CI)
Overall	40.0 (4/10)	12.2 to 73.8	98.8 (1986/2011)	98.2 to 99.2
Acute	66.7 (2/3)	9.4 to 99.2	--	--
Chronic	0.0 (0/4)	0.0 to 60.2	90.5 (105/116)	83.7 to 95.2
Early Recovery	66.7 (2/3)	9.4 to 99.2	96.4 (108/112)	91.1 to 99.0
Recovery	--	--	98.6 (210/213)	95.9 to 99.7
Recovered	--	--	98.8 (326/330)	96.9 to 99.7
HBV Vaccine Response	--	--	100.0 (384/384)	99.0 to 100.0
Not Previously Infected	--	--	99.6 (833/836)	98.9 to 99.9
Uninterpretable	--	--	100.0 (20/20)	83.2 to 100.0

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

A retrospective study was conducted using 49 well-characterized, commercially available samples from patients diagnosed with acute HBV and 105 well-characterized, commercially available 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 corresponding reference assays.

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

	Reference Anti-HBc IgM Assay Negative			Reference Anti-HBc IgM Assay Equivocal / Grey Zone			Reference Anti-HBc IgM assay Positive			
HBV	ADVIA Centaur® HBc IgM Assay			ADVIA Centaur® HBc IgM Assay			ADVIA Centaur® HBc IgM Assay			
Classifi-cation	Reac-tive	Nonreac-tive	Equi-vocal[a]	Reac-tive	Nonreac-tive	Equi-vocal[a]	Reac-tive	Nonreac-tive	Equi-vocal[a]	Total
Acute	0	0	0	2	1	0	46	0	0	49
Chronic	0	105	0	0	0	0	0	0	0	105
Total	0	105	0	2	1	0	46	0	0	154

a   Equivocal results following repeat testing

Positive percent agreement for this population is 97.9% (46/47) and negative percent agreement for this population is 98.1% (105/107).

Seroconversion Study

Six commercially available seroconversion panels were tested with the ADVIA Centaur® HBc IgM assay and a Reference anti-HBc IgM Immunoassay.

A summary of seroconversion results is presented in the following table.

Bayer ADVIA Centaur® HBc IgM Seroconversion Results			
	Detection of anti-HBc IgM by ADVIA Centaur® HBc IgM Assay		
	Earlier than Reference anti-HBc IgM assay	Later than Reference anti-HBc IgM assay	At the same time as Reference anti-HBc IgM assay
Number of Panels	2	0	4

Compared to the Reference assay results, the first reactive time point for the ADVIA Centaur® HBc IgM assay occurred earlier in two panels and at the same time in four panels.

Overall, compared to the Reference anti-HBc IgM assay, the ADVIA Centaur® HBc IgM assay demonstrated efficacy for the detection of the appearance of anti-HBc IgM following HBV infection.

Precision and Reproducibility Study

The ADVIA Centaur® HBc IgM precision and reproducibility study was performed at three external sites utilizing two reagent lots per site. A 5-member panel and controls were assayed in replicates of 5 on a single run per day over six 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.

Bayer ADVIA Centaur® HBc IgM Assay Precision Estimates for All Testing Sites and Reagent Lots									
Panel Member	Mean ADVIA Centaur® HBc IgM Index Value	Within Run[a]		Between Run[b]		Total[c]		No. of Observations	No. of Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
Testing Site Florida, Reagent Lot 93									
1	0.109	0.004	NA	0.002	NA	0.004	NA	30	6
2	0.820	0.033	4.04	0.045	5.48	0.056	6.81	30	6
3	1.660	0.087	5.22	0.080	4.84	0.118	7.12	30	6
4	1.333	0.087	6.53	0.154	11.54	0.177	13.26	30	6
5	5.548	0.378	6.81	1.046	18.85	1.112	20.04	30	6
Negative Control	0.133	0.005	NA	0.046	NA	0.046	NA	30	6
Positive Control	2.798	0.208	7.42	0.176	6.28	0.272	9.72	30	6
Testing Site Florida, Reagent Lot 94									
1	0.188	0.004	NA	0.002	NA	0.005	NA	30	6
2	0.863	0.049	5.68	0.058	6.77	0.076	8.84	30	6
3	1.691	0.131	7.74	0.193	11.40	0.233	13.78	30	6
4	1.548	0.115	7.40	0.184	11.91	0.217	14.02	30	6
5	5.442	0.593	10.90	0.500	9.19	0.776	14.26	30	6
Negative Control	.0172	0.006	NA	0.047	NA	0.047	NA	30	6
Positive Control	2.739	0.171	6.23	0.238	8.69	0.293	10.69	30	6

Testing Site Texas, Reagent Lot 92									
1	0.080	0.003	NA	0.003	NA	0.004	NA	30	6
2	0.821	0.023	2.85	0.030	3.68	0.038	4.66	30	6
3	1.648	0.075	4.55	0.060	3.65	0.096	5.84	30	6
4	1.338	0.058	4.34	0.127	9.49	0.140	10.43	30	6
5	5.871	0.469	7.98	0.517	8.80	0.698	11.88	30	6
Negative Control	0.070	0.002	NA	0.002	NA	0.002	NA	30	6
Positive Control	2.797	0.158	5.64	0.239	8.56	0.287	10.25	30	6
Testing Site Texas, Reagent Lot 94									
1	0.101	0.003	NA	0.009	NA	0.009	NA	30	6
2	0.815	0.035	4.25	0.062	7.60	0.071	8.71	30	6
3	1.706	0.088	5.17	0.079	4.63	0.118	6.94	30	6
4	1.580	0.074	4.70	0.201	12.70	0.214	13.54	30	6
5	6.303	0.524	8.32	0.469	7.44	0.703	11.16	30	6
Negative Control	0.060	0.000	NA	0.000	NA	0.000	NA	30	6
Positive Control	3.221	0.231	7.18	0.249	7.73	0.340	10.55	30	6
Testing Site New York, Reagent Lot 92									
1	0.101	0.005	NA	0.005	NA	0.007	NA	30	6
2	0.825	0.059	7.21	0.073	8.89	0.094	11.45	30	6
3	1.721	0.108	6.30	0.306	17.76	0.324	18.84	30	6
4	1.342	0.146	10.88	0.210	15.61	0.255	19.03	30	6
5	6.075	0.779	12.83	0.384	6.31	0.869	14.30	30	6
Negative Control	0.081	0.003	NA	0.002	NA	0.003	NA	30	6
Positive Control	2.792	0.235	8.42	0.368	13.20	0.437	15.65	30	6
Testing Site New York, Reagent Lot 93									
1	0.070	0.003	NA	0.003	NA	0.004	NA	30	6
2	0.763	0.053	6.98	0.081	10.61	0.097	12.70	30	6
3	1.632	0.102	6.26	0.236	14.48	0.258	15.78	30	6
4	1.325	0.087	6.56	0.141	10.63	0.166	12.49	30	6
5	6.364	0.691	10.87	0.925	14.54	1.155	18.15	30	6
Negative Control	0.060	0.002	NA	0.002	NA	0.002	NA	30	6
Positive Control	2.793	0.170	6.08	0.358	12.83	0.397	14.20	30	6

NA = not applicable

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

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 day.

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

The reproducibility results are presented in the following table:

Bayer ADVIA Centaur® HBc IgM Assay Reproducibility Between Testing Sites and Between Reagent Lots Estimates (Across All Reagent Lots and All Testing Sites)											
Panel Member	Mean ADVIA Centaur® HBc IgM Index Value	Within Run[a]		Between Run[b]		Between Testing Site[c]		Between Lot[d]		Total[e]		Number of Observa-tions
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	
1	0.11	0.004	NA	0.001	NA	0.040	NA	0.014	NA	0.043	NA	180
2	0.82	0.044	5.38	0.021	2.53	0.028	3.47	0.011	1.36	0.057	7.02	180
3	1.68	0.100	5.98	0.072	4.28	0.000	0.00	0.014	0.85	0.124	7.40	180
4	1.41	0.099	7.00	0.066	4.68	0.000	0.00	0.132	9.36	0.178	12.59	180
5	5.93	0.588	9.91	0.198	3.33	0.473	7.97	0.000	0.00	0.780	13.15	180
Negative Control	0.10	0.003	NA	0.012	NA	0.055	NA	0.000	NA	0.056	NA	180
Positive Control	2.86	0.198	6.92	0.097	3.40	0.189	6.63	0.000	0.00	0.291	10.17	180

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.
NA = Not applicable
Note: 5 replicates per panel in 1 run per day for 6 days

Paired Matrix Study

Using patients from the prospective population, matched serum, EDTA, and lithium heparin specimens were collected to demonstrate that use of different matrices had no significant effect on the device's results. Serum and plasma were tested in replicates of three per sample type using the ADVIA Centaur® HBc IgM assay and appropriate assay controls. EDTA and lithium heparin were evaluated against serum (control) to determine matrix equivalency.

Results of the Paired Matrix Study support the use of EDTA and lithium heparin as anticoagulants. Samples collected with EDTA show 0% bias when compared to serum, and samples collected with lithium heparin show 0% *total* bias when compared to serum by using *nested* SAS statistical software (see caution below). Comparisons of the mean control serum Index Value to the mean lithium heparin Index Value and the mean EDTA Index Value showed no apparently significant differences. Results of the paired matrix study are summarized in the

following table and in a commentary following the summary table.

Bayer ADVIA Centaur® HBc IgM Assay Matrix Study Summary (All Testing Sites)	
Specimen Type	**Mean ADVIA Centaur® HBc IgM Index Value Value**
Serum (control)	0.18
EDTA plasma	0.18
Lithium heparin plasma	0.18
Difference in Mean ADVIA Centaur® HBc IgM Index Value Value	
Control vs. EDTA	Control vs. Heparin
0.00 (p = 0.9375)[a]	0.00 (p = 0.9128)[a]
a P-value for the comparison of difference of Mean Serum Control Index Value versus Mean Heparin/EDTA Index Value (Two-sample comparison: t-Test, Wilcoxon Rand Test, or Exact Wilcoxon Test as appropriate after testing for normality and sample size).	

NOTE: Because some results from the specimen matrix comparison study performed in-house indicated a potential bias in heparin specimens, the following statement was placed in the Specimen Collection section of the product insert.

CAUTION: Heparin has been shown to increase Index Values in some HBc IgM reactive samples by up to 28% relative to serum .Results falling near the cutoff should be repeated with a serum specimen or interpreted with caution.

Interpretation of Clinical Studies

The following pattern of result interpretation was established on the basis of information collected from the clinical studies of the ADVIA Centaur® HBc IgM assay:

Result Interpretation Using ADVIA Centaur® HBc IgM assay		
ADVIA Centaur® HBc IgM Assay Result	**Status**	**Interpretation**
<0.80	Nonreactive	Patient does not have a detectable level of HBc IgM antibody.
≥0.80 and <1.00	Equivocal	Unable to establish if HBc IgM is present at levels correlating with acute or recent HBV infection. Other clinical information is required to further assess patient's clinical status.
≥1.00	Reactive	Patient is considered reactive for HBc IgM. (patient may be considered to have an acute or recent HBV infection when tested in conjunction with other HBV markers and clinical findings.)

Study Design

Gender Bias

1. The selection ratio of men versus women in the study was similar and was reflective of the underlying distribution of the disease for each given age group, ethnic group, stage of disease, etc. 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. Because of this, results may only be reported in % positive and % negative results which is statically appropriate where there may selection, gender bias.

2. 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.

Patient Assessments:

Demographic Data -2021 patient samples were run in the ADVIA Centaur HBc IgM assay. The following results classified by gender and age range were obtained:

Age Range (Years)	Gender	Reactive (N)	Reactive (%)	Nonreactive (N)	Nonreactive (%)	Equivocal (N)	Equivocal (%)	Total
0-9	M	0	--	0		0	--	0
	F	0	--	0		0	--	0
10-19	M	0	--	7	100.00	0	--	7
	F	0	--	14	100.00	0	--	14
20-29	M	1	1.19	83	98.81	0	--	84
	F	2	2.00	98	98.00	0	--	100
30-39	M	2	1.02	193	98.47	1	0.51	196
	F	2	1.08	183	98.92	0	--	185
40-49	M	7	1.82	376	97.92	1	0.26	384
	F	1	0.34	295	99.33	1	0.34	297
50-59	M	6	2.08	281	97.57	1	0.35	288
	F	2	0.97	204	99.03	0	--	206
60-69	M	1	1.15	86	98.85	0	--	87
	F	1	1.01	98	98.99	0	--	99
>/=70	M	2	4.44	43	95.56	0	--	45
	F	0	--	28	100.00	0	--	28
Unknown	M	0	--	1	100.00	0	--	1
	F	0	--	0	--	0	--	0
Total		27	1.34	1990	98.46	4	0.20	2021

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Multi-centered clinical studies were conducted in the US. The ADVIA Centaur® HBc IgM assay performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

- Hepatitis B virus classification using the prospective population showed 31 unique reference marker patterns. The overall positive percent agreement between the ADVIA Centaur® HBV assay and the reference anti-HBc IgM assay was 40% in the high risk, signs and symptoms, and dialysis populations combined. The positive percent agreement for prospective population acute samples was 66.67% (2/3). The overall negative percent agreement between the ADVIA Centaur® HBc IgM assay and the reference assay was 98.81% in the high risk, signs and symptoms, and dialysis populations combined. Specimens with an equivocal result in either the ADVIA Centaur® HBc IgM assay (n = 3) or the Reference anti-HBc IgM assay (n = 15) were treated as discrepants for the purpose of calculating positive and negative percent agreement. The one specimen which was equivocal for both the ADVIA Centaur® HBc IgM assay and the Reference anti-HBc IgM assay was treated as a nonreactive concordant sample.

- In the HBV infected acute and chronic retrospective population, the overall positive percent agreement was 97.87% (46/47) and the overall negative percent

agreement was 99.06% (105/106). The two discrepant samples were equivocal in the Reference assay but were considered discrepant for statistical purposes.

- The ability of the ADVIA Centaur® HBc IgM assay to detect HBV infections early was demonstrated with the seroconversion panel evaluation. When the ADVIA Centaur® HBc IgM result was compared to the Reference assay results, the first reactive time point for the ADVIA Centaur® HBc IgM assay occurred earlier in 2 panels and at the same time in 4 panels.

- Precision and reproducibility of the ADVIA Centaur® HBc IgM assay was good with minor variability from run to run, day to day, or reagent lot to reagent lot.

- Paired Matrix Study results support the use of human serum, EDTA plasma, and lithium heparin plasma specimens for testing in the ADVIA Centaur® HBc IgM assay.

The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur® HBc IgM assay can be used safely and effectively for the qualitative in vitro determination of HBc IgM in human serum and plasma. The ADVIA Centaur® HBc IgM assay 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 viral hepatitis.

RISK BENEFIT ANALYSIS

As a diagnostic test, the ADVIA Centaur ® HBc IgM Assay involves removal of blood from an individual for testing purposes. This test presents no more of a safety hazard to an individual who is having their blood drawn for any other diagnostic evaluations. The benefits to HBV infected individuals tested by these assays outweigh any potential adverse event or risk to the patient or user due to assay malfunction or operator error.

The potential risks encountered with *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 end user.

SAFETY

The safety of the ADVIA Centaur® HBc IgM is acceptable, as it is used in conjunction with other serological markers. No clinical assessment or treatment decisions should be made based on the results of the ADVIA Centaur® HBc IgM alone.

EFFECTIVENESS

The effectiveness of the ADVIA Centaur® HBc IgM has been demonstrated for use in determining if HBc IgM is present in an individual's serum or plasma. A reasonable determination of effectiveness of the ADVIA Centaur® HBc IgM assay for aiding in the diagnosis of acute HBV infection has been demonstrated

XII.   PANEL RECOMMENDATION

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 Microbiology Devices Panel, an FDA advisory committee, for review and recommendation because the

information in the PMA substantially duplicates information previously reviewed by this panel.

XIII.   CDRH DECISION

FDA issued an approval order on August 6, 2004.

The applicant's manufacturing facility was inspected on October 27, 2003 and November 13, 2003 and found to be in compliance with the Quality Systems Regulation (21 CFR 820).

XIV.   APPROVAL SPECIFICATIONS

Directions for use: See the package 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.