SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS

I GENERAL INFORMATION

Device Generic Name:	Total Antibody to Hepatitis B Core Antigen (Anti-HBc Total Assay)
Device Trade Name:	ADVIA Centaur® HBc Total Assay ADVIA Centaur® HBc Total Quality Control
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:	P040004
Date of Notice of Approval to Applicant:	December 22, 2004

II. INDICATIONS FOR USE

ADVIA Centaur HBc Total Assay

The ADVIA Centaur HBc Total assay is an *in vitro* diagnostic test for the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBcTotal) in human serum or plasma (potassium EDTA, or lithium or sodium heparinized) using the ADVIA Centaur®. System. This assay can be used as an aid in the diagnosis of individuals with acute or chronic hepatitis B virus (HBV) infection and in the determination of the clinical status of HBV infected individuals in conjunction with other HBV serological markers for the laboratory diagnosis of HBVdisease associated with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

HBc Total Quality Control

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

III. CONTRAINDICATIONS : None known

IV. WARNINGS AND PRECAUTIONS

For *in vitro* diagnostic use only.

Warnings and precautions for ADVIA Centaur® HBc Total ReadyPack Reagents and ADVIA Centaur® HBc Total Quality Control Materials are stated in the respective product labeling.

V. DEVICE DESCRIPTION

Assay Principle and Format

The ADVIA Centaur® HBc Total assay is a 2-wash antigen sandwich immunoassay in which antigens are bridged by antibody present in the patient sample. The Solid Phase contains a preformed complex of streptavidin coated microparticles and biotinylated recombinant HBc antigen (rHBcAg) and is used to capture antibodies to HBc (anti-HBc) in the patient sample.

Sample is first incubated for 6 minutes at 37°C. The Solid Phase is added next and the reaction mix incubates for 18 minutes at 37°C. During this incubation rHBcAg on the micropartcles bind to the anti-HBc antibodies in the sample. A chaotrope is also added to prevent non-specific binding. The microparticles are then held fast by a magnet and washed multiple times to remove unbound sample. More chaotrope is added and the reaction mix is incubated for 6 minutes. Lite reagent consisting of rHBcAg conjugated to Acridinium ester is added next and the reaction mix incubates for 18 more minutes at 37°C. 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 quantified as relative light units (RLUs) by the photomultiplier tube (PMT) of the ADVIA Centaur Instrument. The relative light units (RLUs) detected by the ADVIA Centaur System are used to calculate the Index Value from the Master Curve. A result of reactive or nonreactive is determined according to the Index Value established with the calibrators. The Master Curve values are contained on the Master Curve card provided with each kit.

Assay antigen/antibody Description

The ADVIA Centaur® HBc Total assay utilizes biotinylated rHBcAg that is complexed to streptavidin-coated microparticles in the Solid Phase. The Lite Reagent utilizes rHBcAg labeled with AE to detect anti-HBc that was captured by the complex of biotinylated rHBcAg and streptavidin-coated microparticles.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Determination of the presence of anti-HBc IgM and/or anti-HBc IgG 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 Total Assay is currently being marketed internationally in accordance with section 802 of the FD&C Act.

The Americas: Colombia
Europe: Sweden, Norway, Finland, France, Germany, Italy. Spain, Portugal, UK, Belgium, Austria
Africa: South Africa
Asia: Japan, China, Hong Kong, Singapore, Malaysia, Korea, Australia, New Zealand

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ADVIA Centaur® HBc Total ReadyPack Reagents and ADVIA Centaur® HBc Total Quality Control Materials are for in vitro diagnostic use, thus there is no direct adverse effect on the patient.
Failure of the product to perform as intended, or errors in the use of the product, may lead to a false result. This assay is used as an aid in the diagnosis of individuals with acute or chronic HBV infection and in the determination of the clinical status of HBV infected individuals in conjunction with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.
A false nonreactive result does not exclude the possibility of exposure to HBV. A nonreactive result may be due to antibody levels below the detection limits of this assay. Since this assay is used in combination with other HBV assays, a nonreactive result cannot be considered a public health risk, as the individual would be tested with other methodologies if signs and symptoms are indicative of HBV infection.
A false reactive result would not be considered a public health risk due to the fact that an individual would be tested with other hepatitis B virus marker assays to define the clinical status of the patient.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

Objectives. The objectives of the laboratory studies were to test the ADVIA Centaur® HBc Total performance with respect to: Analytical Sensitivity, Potential Cross-Reactive Specimens, Endogenous Interferents, Precision Studies, and Effects of Type of Collection Tube on Matrix Data, Sample Handling Studies, Stability Studies, Microbiology Studies, and Instrument Studies.

Analytical Sensitivity

The concentration of Paul Ehrlich Institute (PEI) anti-HBc Total reference unit that corresponds to the cutoff Index (0.50) of the ADVIA Centaur® HBc Total assay was determined. A dilution series was prepared in negative plasma base-pool and tested using 2 pilot lots of anti-HBc Total reagents. The estimates of PEI concentration at the cutoff value of 0.50 Index ranged from 0.19 PEI IU to 0.22 PEI IU.

Potential Cross-Reactive Specimens

The ADVIA Centaur HBc Total assay was evaluated for potential cross-reactivity with other viral antibodies and disease state specimens. The anti-HBc Total status of each specimen was verified using an anti-HBc Total reference assay. The following results were obtained using the ADVIA Centaur HBc Total assay.

Clinical Category	*Number Tested*	*Number of Positive Anti-HBc Total Results*	
		ADVIA Centaur Assay	*Reference Assay*
Hepatitis A Infection (HAV)	5	1	1
Hepatitis C Infection (HCV)	10	4	4
Epstein-Barr Virus (EBV) IgG	10	2	2
Epstein-Barr Virus (EBV) IgM	10	3	3
Herpes Simplex Virus (HSV) IgG	10	3	3
Herpes Simplex Virus (HSV) IgM	10	4	4
Cytomegalovirus IgG	10	7	7
Cytomegalovirus IgM	3	1	1
Toxoplasma IgG	10	2	2
Toxoplasma IgM	7	0	0
Syphilis IgG	10	1	1
Human Immunodeficiency Virus (HIV1/2)	10	2	2
Varicella Zoster IgG	10	4	4
Rubeola IgG	10	5	4[1]
Non viral Liver Disease	9	0	0
Autoimmune Disease (Rheumatoid Arthritis)	9	0	0
Anti-Nuclear Antibody (ANA)	5	1	1
Systemic Lupus Erythematosus (SLE)	2	0	0
HAMA	10	0	0

Clinical Category	*Number Tested*	*Number of Positive Anti-HBc Total Results*		
		ADVIA Centaur Assay		*Reference Assay*
Flu vaccine Recipient	10	3		3
Total Samples Tested	170	43		42

1. The non-confirmed ADVIA Centaur HBc Total reactive result was ADVIA Centaur anti-HBs positive.

Endogenous Interferents

The potentially interfering effects of conjugated bilirubin, unconjugated bilirubin, hemoglobin, triglycerides, hyper IgG and low protein were evaluated for interference due to endogenous substances.

Serum specimens that are ...	***Demonstrate ≤ 10% change in results up to ...***
hemolyzed	500 mg/dL of hemoglobin
lipemic	1000 mg/dL of intralipids
icteric	60 mg/dL of conjugated bilirubin
icteric	40 mg/dL of unconjugated bilirubin
hyperproteinemic	12.0 g/dL of protein
hypoproteinemic	3.5 g/dL of protein
Hyper IgG	600 mg/mL of immunoglobulin G

Precision Studies

Precision was evaluated according to the National Committee for Clinical Laboratory Standards protocol EP5-A. A 6 member panel and controls were assayed in 2 replicates, 2 times a day, for 20 days. The Table below shows the results obtained using 1 reagent lot and a stored calibration curve.

Table 3: Centaur® HBc Total precision

Sample	Mean Index Value	Within-run SD	CV(%)	Run-to-run SD	CV(%)	Total SD	CV(%)
Serum 1	0.06	0.02	NA*	0.01	NA	0.02	NA
Serum 2	1.13	0.06	5.1	0.05	4.5	0.09	8.4
Serum 3	1.22	0.04	3.6	0.05	4.2	0.08	6.8
Serum 4	1.35	0.08	5.8	0.05	3.8	0.10	7.1
Serum 5	2.40	0.12	4.9	0.08	3.4	0.19	7.7
Serum 6	4.54	0.20	4.4	0.21	4.7	0.29	6.5
Plasma							
Control Low	0.45	0.03	6.7	0.02	3.4	0.04	8.0
Control High	3.69	0.12	3.3	0.13	3.3	0.22	6.0

NA*=Not applicable

Effects of Type of Collection Tube on Matrix Data

Blood was collected during in-house blood draws from 50 healthy, normal donors in Red Top (serum), SST (serum), potassium EDTA (plasma), sodium heparin (plasma), and lithium heparin (plasma) collection tubes. A total of 49 donor samples were nonreactive in the ADVIA Centaur® HBc Total assay, 1 donor was found to be anti-HBc reactive. A total of 29 samples that were nonreactive were spiked with pooled plasma from individuals that had high titers of anti-HBc as determined by the ADVIA Centaur® HBc Total assay. Spiking volume was varied among samples in order to create a positive pool that represented the full dynamic range of the assay. The results demonstrated that, for the anticoagulants tested, Index values were similar among samples in different collection tubes. Also, Index values among negative samples were similar. For donors that were anti-HBc positive, there was no change in clinical interpretation when samples were tested using different collection tubes. In conclusion, these collection tubes are acceptable for use with the ADVIA Centaur® HBc Total assay. Serum, EDTA plasma, lithium or sodium heparinized plasma are the recommended sample types for this assay. Heparin has been shown to decrease the Index values in some HBc Total reactive samples. Results obtained from heparin specimens falling near the cutoff should be repeated with a serum specimen or interpreted with caution.

Sample Handling Studies

The sample handling studies are a series of experiments in which specimens collected in all of the possible sample matrices are tested using the ADVIA Centaur® HBc Total assay. These sample matrices include conditions that are claimed as suitable for use in the ADVIA Centaur® HBc Total method. Samples are subjected to potential stresses such as freeze/thaw or elevated temperature storage and tested in comparison to baseline data to determine the impact of the

stress on assay accuracy. A baseline Index value for each sample was established by testing with the ADVIA Centaur® HBc Total assay on the day of collection. All percentage recoveries are calculated against the baseline (day 0) value. Results from the ADVIA Centaur® HBc Total sample handling studies support the claims that samples can be subjected to the following conditions and still generate accurate results when tested in the ADVIA Centaur® HBc Total assay:

1. Samples can be kept onboard the Centaur® instrument for up to 24 hours.
2. Samples can be stored refrigerated (2-8°C) for up to 3 days.
3. Samples can be stored at room temperature for up to 12 hours.
4. Samples can be stored frozen (-20°C) for long-term storage.
5. Samples can be frozen and thawed up to 2 times

Sample Processing – Time to Centrifugation

A study was done to determine the effect of fresh sample time-to-centrifugation on the anti-HBc Total Index. Samples were drawn from 10 healthy in-house donors in serum and EDTA plasma collection tubes. Seven donor tubes were spiked with anti-HBc Total positive pool, 3 donor tubes remained negative. Spiking was performed prior to centrifugation. Aliquots were centrifuged immediately after collection (time 0), and at 6 hours and 24 hours after collection, and tested in the Centaur® HBc Total assay. The recovery of anti-HBc Index Value in donor samples that were centrifuged at 6 and 24 hours after collection varied from 82% to 129% of the time 0 Index Value. The clinical status of the sample was the same regardless of time of centrifugation or tube type. In conclusion, samples processed by centrifugation up to 24 hours post draw demonstrated no qualitative differences in the Centaur® HBc Total assay.

Sample Handling – Inversion of Gel barrier Collection tubes

A study was done to determine if inversion of barrier gel blood collection tubes interferes with ADVIA Centaur® HBc Total assay results. Blood was drawn from 10 healthy in-house donors using serum and plasma (lithium heparin) gel barrier (separator) collection tubes. Seven sample tubes were spiked with anti-HBc at different levels, and the remaining 3 were left negative. The tubes were rotated for 30 minutes, centrifuged, and an aliquot was taken. The tubes were then inverted 5 times and a second aliquot was taken. The 2 aliquots were compared to determine if inversion altered sample Index value in the ADVIA Centaur® HBc Total assay. The inversion had no effect on the serum samples. However, Index values were not similar before and after inversion for samples collected in PST and lithium heparin tubes unless the sample was centrifuged after inversion and

prior to testing in the ADVIA Centaur® HBc Total assay. In conclusion, samples collected in gel barrier tubes need to be centrifuged prior to testing in the ADVIA Centaur® HBc Total assay.

Stability Studies

Real Time Stability Studies for ADVIA Centaur® ReadyPack reagents:

Two manufactured lots of HBc Total reagents were tested in real-time stability studies. All kits and reagents are stored at the recommended storage temperature of 2 to 8°C. Reagents were monitored at several checkpoints post manufacturing date. Results of these stability studies support a shelf-life of 52 weeks for the HBc Total ReadyPack reagents.

Reagent Onboard Stability (OBS) Studies:

Two lots of reagents have undergone reagent OBS studies on 1 ADVIA Centaur® instrument. Onboard stability testing on the instrument occurred at several time points after the reagent was placed onboard. A fresh (unopened) pack served as the control for each time-point. Dose recovery within 10% or 2 standard deviations of the fresh pack was defined as acceptable performance. Similarly, evaluation of the dose recovery of the opened pack versus the fresh pack defines the interval between calibrations on the Centaur® instrument. The onboard studies for the reagents supported an OBS of 28 days for the ADVIA Centaur® HBc Total reagents. The OBS studies also supported a recalibration interval of 14 days.

Reagent Shipping Studies:

Shipping studies demonstrated that the ADVIA Centaur® HBc Total reagents provided acceptable performance after 3 freeze/thaw cycles (-20°C to 4°C). No aggregation of the solid phase was observed in these studies. Testing of upside-down shipping was also performed. ReadyPack reagents stored upside down for up to 8 weeks provided acceptable performance. The recommended shipping and storage conditions are upright at 2°C to 8°C.

Real-time stability studies of lots of calibrators and controls for the ADVIA Centaur® HBc Total assay:

Two lots of calibrators and controls were stored at 2°C to 8°C for long-term stability studies and monitored at several checkpoints post manufacturing date. Results of these stability studies support a shelf-life of 52 weeks for the HBc Total calibrators and controls.

Open-bottle stability tests of the calibrator and controls for the ADVIA Centaur® HBc Total assay:

The length of time that the calibrator and controls were stable in open containers was investigated. Open vials were stored at the recommended storage conditions

of 2°C to 8°C. The open containers were sampled periodically for up to 62 days after opening. Fresh (unopened) bottles 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 dose recovery observed using samples from the fresh container. The study supports an open bottle use lifetime of up to 62 days.

Shipping stability studies of the ADVIA Centaur® HBc Total calibrators and controls:

No loss of performance was observed after calibrators and controls from 1 lot underwent 3 freeze/thaw cycles.

Microbiology Studies

The ADVIA Centaur HBc Total reagents and calibrators contain 0.2% Micr-O-Protect and the ADVIA Centaur HBc Total controls contain 0.1% Proclin 300 and 0.09% sodium azide as a preservative to protect against adventitious contamination by microorganisms. Reagents, calibrators and controls were challenged in a study conducted according to USP requirements for Antimicrobial Effectiveness testing to assess the ability of the reagents to withstand or control microbial contamination. The test involved seven microorganisms. Results indicated that the preservative systems for reagents and calibrators met the USP requirements for antimicrobial effectiveness testing. The preservative study results for controls indicated inhibition of growth of the USP challenge organisms except for *C. piscicola.* The latter showed a slight growth in the first two weeks of the six week study.. No clinically significant changes in Index values were observed after using inoculated reagents versus control reagents.

Instrument Studies

(1) Environmental Testing:

The purpose of environmental testing was to assess ADVIA Centaur® HBc Total assay recovery at the mean and extreme environmental conditions as specified. Each assay was calibrated and run on a single unit in an environmental chamber set at 18°C, 24°C and 30°C. The percent change in control recovery per degree centigrade was calculated. ADVIA Centaur® HBc Total assay environmental testing data satisfied the general specification of less than 10% change of Index value versus control conditions over a 6°C deviation in ambient temperature.

(2) Reagent Compatibility Testing:

The purpose of this study was to confirm that there were no interactions

between reagents that share the same reagent probe and reagents that may have caused carryover effects in separate assays. Mitigation of any interference identified was accomplished through Test definition (TDef) scheduling options, using multiple water washes, or, in rare occasions, by using a Wash Pack with a solution other than water.

The ADVIA Centaur® HBc Total assay was evaluated for its potential effect on all other assays using the same reagent probes, and the effect of all the other assay reagents on the anti-HBc Total assay was evaluated. To be accepted there must have been <5% difference in dose between test and control; or no statistically significant change in dose; or no more than 1 standard deviation 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 that shared the same reagent probe.

Conclusions Drawn from the Non-Clinical Studies

The ADVIA Centaur® HBc Total assay was evaluated to demonstrate performance claims for cross-reactivity, interference, precision, matrix type, specimen handling, and reagent stability.

X. SUMMARY OF CLINICAL STUDIES

The objective of this clinical study was to assess the efficacy of ADVIA Centaur® HBc Total for detecting antibody (IgG and IgM) against HBc antigen in human serum or plasma as presumptive evidence of an HBV infection.

Study Design

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

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® HBc Total assay and a reference HBc Total assay at the clinical trial sites.

A study of retrospectively (commercial vendor) obtained samples from HBV acutely infected and HBV chronically infected patients. Vendor assignment of HBV acute samples was based upon positive HBsAg and HBc IgM assay results. 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® HBc Total assay and a reference HBc Total assay at the clinical trial sites.

A study of retrospectively (commercial vendor) obtained HBV seroconversion panels. These panels were tested with both the ADVIA Centaur® HBc Total assay and a reference HBc Total assay at the clinical trial sites.

A precision and reproducibility study in which a specimen panel was assayed over several days, at multiple clinical trial sites, and using multiple ADVIA Centaur® HBc Total assay reagent lots. The results were analyzed to derive precision estimates.

A paired matrix study in which a subset of the prospectively obtained High Risk, Signs and Symptoms, and Dialysis samples was collected in serum, EDTA plasma, and lithium heparin plasma collection tubes. The samples from all collection tube types were then compared by testing in the ADVIA Centaur® HBc Total assay.

These studies are described in detail below.

Bayer ADVIA Centaur® HBc Total Assay
Distribution of High Risk, Signs and Symptoms, and Dialysis Population by Age Group and Gender
All Testing Sites

Age (years)	Gender	Reactive[a]		Nonreactive[b]		Total	
		N	%	N	%	N	%
0-9	Male	0	--	0	--	0	--
	Female	0	--	0	--	0	--
	Overall	0	--	0	--	0	--
10-19	Male	2	28 57	5	71.43	7	31.82
	Female	1	6 67	14	93.33	15	68.18
	Overall	3	13.64	19	86.36	22	100.00
20-29	Male	15	17.86	69	82.14	84	45.65
	Female	16	16.00	84	84.00	100	54.35
	Overall	31	16.85	153	83.15	184	100 00
30-39	Male	77	39 29	119	60.71	196	51.44
	Female	51	27.57	134	72.43	185	48.56
	Overall	128	33.60	253	66.40	381	100.00
40-49	Male	216	56 10	169	43.90	385	56.45
	Female	106	35.8	190	63.97	296	43.46
	Overall	322	47.28	359	52.64	681	100.00
50-59	Male	172	60.35	113	39.24	285	58.40
	Female	76	37.43	127	61.95	203	41.59
	Overall	248	50.82	240	48.68	488	100.00
60-69	Male	37	43.02	49	56.32	86	46.52
	Female	28	28.00	72	72.00	100	53.48
	Overall	65	34.95	121	64.71	186	100.00
≥70	Male	21	46.67	24	53.33	45	61.64
	Female	5	17.86	23	82.14	28	38.36
	Overall	26	35.62	47	64.38	73	100.00
Unknown	Male	1	100.00	0	--	1	100.00
	Female	0	--	0	--	0	--
	Overall	1	100.00	0	--	1	100.00
Total	Male	541	49.67	548	50.14	1089	54.02
	Female	283	30 53	644	69.25	927	45.98
	Overall	824	40.87	1192	58.92	2016	100.00

a Samples with an Index Value ≥ 0.50
b Samples with an Index Value < 0 50

Gender Bias

1. The selection ratio of men versus women in the High Risk, Signs and Symptoms & Dialysis prospective 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 which is statistically appropriate where there may be 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.
3. Demographic Data – 2016 patient samples were run in the ADVIA Centaur® HBc Total assay. The following results classified by gender and age range were obtained:

Data Analysis and Results

Prospective Study

The prospective study population for the ADVIA Centaur® HBc Total assay consisted of 2016 patients. Of these 2016 patients, 961 patients (47.67%) were from the high risk population, 844 patients (41.87%) were from the signs and symptoms population, and 211 patients (10.46%) were from the dialysis population. The prospective study population was 42.56% Caucasian, 26.54% Hispanic,. 23.31% Black, 3.26% Asian, and 4.30% from unknown or other ethnicity. The majority of patients were male (54.02% male and 45.98% female). The mean age was 45.9 years (range of 12 to 82 years). Patients in the prospective study population were from the following geographic regions: Florida (38.79%), Texas (33.18%), New York (19.62%), and California (8.33%).

The HBV disease classification for each patient in the high risk, signs and symptoms, and dialysis populations (2016 patients total) was determined by serological assessment using resultant hepatitis marker profiles obtained from results of commercially available, USFDA-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 virus 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. No patients were excluded from the complete study set because of incomplete reference HBV serological results.

Each patient's HBV infection was classified based on the reactive (+)/nonreactive(-) patterns of the 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 31 unique reference marker patterns. These patterns are presented in the following table.

HBV Classification	HBsAg[a]	HBeAg	Anti-HBc IgM	Anti-HBc Total	Anti-HBe	Anti-HBs (>10mIU/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 positive by neutralization
nonreactive (-) = reference HBsAg assay results was nonreactive or reactive but not confirmed positive by neutralization.

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

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 and nonreactive). The method comparison for all testing sites combined is presented in the following table.

Method Comparison in High Risk, Signs and Symptoms, and Dialysis Population by HBV Classification

ADVIA Centaur® HBc Total Assay vs. anti-HBc Total Reference Assay

All Testing Sites

	Reference anti-HBc Total Negative		**Reference anti-HBc Total Positive**		**Total** [a]
	ADVIA Centaur® HBc Total Assay		**ADVIA Centaur® HBc Total Assay**		
	Reactive	**Nonreactive**	**Reactive**	**Nonreactive**	
HBV Classification	**N**	**N**	**N**	**N**	**N**
Acute	0	0	11	0	11
Chronic	0	0	111	1	112
Early Recovery	0	0	123	0	123
Recovery	1	1	208	1	211
Recovered	0	0	269	51	320
HBV Vaccine Response	15	368	0	0	383
Not Previously Infected	27	808	0	0	835
Uninterpretable	1	14	6	0	21
Total	44	1191	728	53	2016

a Total number of test results by HBV categories

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 =

$$\frac{\text{Number of ADVIA Centaur® HBc Total reactive results in agreement with reference anti-HBc Total}}{\text{Total number of reference anti-HBc Total reactive results}} \times 100$$

Negative percent agreement =

Number of ADVIA Centaur® HBc Total nonreactive results in agreement with reference anti-HBc Total X 100
Total number of reference anti-HBc Total nonreactive results

Overall percent agreement =

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

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

Bayer ADVIA Centaur® HBc Total Assay

Percent Agreement and Confidence Intervals by HBV Classification in High Risk, Signs and Symptoms, and Dialysis Population

ADVIA Centaur® HBc Total Assay vs. anti-HBc Total Reference Assay

All Testing Sites

HBV Classification	Positive Percent Agreement % (x/n)[a]	95% Confidence Interval	Negative Percent Agreement % (x/n)[b]	95% Confidence Interval
Acute	100.00 (11/11)	71.51 to 100.00	--	--
Chronic	99.11 (111/112)	95.13 to 99.98	--	--
Early Recovery	100.00 (123/123)	97.05 to 100.00	--	--
Recovery	99.52 (208/209) *	97.36 to 99.99	50.00 (1/2)**	1.26 to 98.74
Recovered	84.06 (269/320)***	79.58-87.90	--	
HBV Vaccine Response	--		96.08 (368/383)	93.62-97.79
Not Previously Infected	--		96.77(808/835)	95.33-97.86
Uninterpretable	100.00 (6/6)	54.07 to 100.00	93.33 (14/15)	68.05 to 99.83
Overall	93.21 (728/781)	91.22 to 94.88	96.43 (1191/1235)[c]	91.90 to 97.65

a x = the number of ADVIA Centaur® HBc Total results that are reactive in agreement with the
reference anti-HBc Total; n = the total number of reference anti-HBc Total results that are reactive

b x = the number of ADVIA Centaur® HBc Total results that are nonreactive in agreement with the
reference anti-HBc Total; n = the total number of reference anti-HBc Total results that are nonreactive

These samples were tested with a second FDA approved anti-HBc assay with the following results (see discussion below) :

*Recovery - 1 discrepant sample was reactive when tested with a 2nd FDA approved assay

**Recovery - 1 discrepant sample was reactive when tested with a 2nd FDA approved assay

***Recovered - 22 of 51 discrepant samples were non-reactive when tested with a 2nd FDA approved assay

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 104 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. Positive percent agreement and negative percent agreement for this population were both 100.0%.

Seroconversion Study

Commercially available HBV patient seroconversion panels were tested using the ADVIA Centaur HBc Total assay to determine the seroconversion sensitivity of the assay. The following results were obtained:

	Anti-HBc Total Positive Result From Initial Draw Date		***Reference Assay vs. ADVIA Centaur Assay Difference in Bleed Numbers****
Panel ID	***Reference Assay (Days)***	***ADVIA Centaur Assay (Days)***	
RP-009	29	29	0
RP-0016	60	57	+1
RP-0017	71	71	0
BCP-6281	41	41	0
Nabi-SB0413	62	62	0
Nabi-SB0411	35	35	0
Serological s 22663D	63	63	0

The difference in bleed numbers is relative to the reference assay. For example, a +1 means that the reference assay required 1 additional bleed before reactivity was determined as compared to the time-point when ADVIA Centaur assay confirmed positive.

Precision and Reproducibility Study

The ADVIA Centaur® HBc Total reproducibility study was performed at 3 external sites using 2 reagent lots per site. A twenty member panel and controls were assayed in replicates of 5 on a single run per day over 6 days for each lot. The study was completed within a single calibration of the assay (one calibration interval). The maximum number of replicates used was 180. Control Lot 782174 was used at two sites and the reproducibility analyses for this lot included 120 replicates. A 2nd Control lot, 783154, was used at only one site and the reproducibility analyses for this lot included 60

replicates. Replicates of negative samples (Panel member 1) reported as below the reportable range were non-numerical results and were excluded from the analyses. Eight positive panel member results were determined to be outliers and were excluded from the analyses. The data from all 3 sites and from all 3 reagent lots were combined to obtain SD and percent CV for within run, between run, between testing site, between reagent lot, and total. The precision estimates were derived from variance component analysis. A NESTED SAS model was used for analysis. The reproducibility results are presented in the following table.

Bayer ADVIA Centaur HBcT Index Reproducibility Between Reagent Lots and Testing Sites

Panel Member or	Matrix or	Mean	Within Run[a]		Between Run[b]		Between Site[c]		Between Reagent Lot[d]		Total[e]		Number of
Control Level	Control Lot	Index Value	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	Observations
1	EDTA	0 10	0 01	N/A	0 01	N/A	0.04	N/A	0 03	N/A	0 05	N/A	177
1	Li Heparin	0.09	0 02	N/A	0 01	N/A	0.03	N/A	0 02	N/A	0 04	N/A	156
1	Na Heparin	0 08	0 01	N/A	0 00	N/A	0 02	N/A	0 03	N/A	0 04	N/A	150
1	Serum	0.08	0 02	N/A	0 01	N/A	0 02	N/A	0 03	N/A	0 04	N/A	158
2	EDTA	0 71	0.04	6 2	0 04	5 8	0 05	6 7	0 02	2.8	0 08	11 2	180
2	Li Heparin	0 69	0.04	6 5	0 05	6 6	0 03	5 0	0 04	5.3	0 08	11 8	180
2	Na Heparin	0 64	0 05	7 9	0 05	7.5	0 06	9 9	0 00	0 0	0.09	14 8	180
2	Serum	0 68	0.04	6 4	0.06	8 3	0 02	3 0	0 05	7.2	0 09	13 1	180
3	EDTA	0 77	0 05	6.5	0 06	7.3	0 03	4 2	0.03	4.4	0 09	11 5	180
3	Li Heparin	0 75	0 05	7.3	0 06	7.4	0 03	4 2	0 03	3.4	0 09	11 7	175
3	Na Heparin	0 70	0 05	7 1	0.03	4 9	0.06	9 1	0.00	0.0	0 09	12 5	180
3	Serum	0.75	0 05	6.1	0 06	8 7	0.02	3 1	0.04	5.0	0.09	12 1	180
4	EDTA	1 09	0 08	7 7	0 07	6 7	0 07	6 8	0.06	5.3	0 15	13 4	180
4	Li Heparin	1.03	0 07	6 8	0 05	5 0	0.08	7.6	0 07	6.8	0 14	13 2	180
4	Na Heparin	0.98	0 07	6 8	0 07	6 9	0.08	7.8	0 00	0 0	0 12	12 5	180
4	Serum	1.07	0 07	6 6	0.11	10 3	0 00	0.0	0 05	4 7	0 14	13 1	180
5	EDTA	2.75	0 16	6 0	0.20	7 4	0 14	5 0	0 17	6 0	0 34	12 3	179
5	Li Heparin	2.73	0 15	5 7	0 15	5 6	0 17	6 3	0 15	5 6	0 32	11 6	180
5	Na Heparin	2.57	0 12	4 8	0 15	5 8	0.15	6 0	0 00	0 0	0 25	9 6	178
5	Serum	2.78	0 19	6 9	0 22	8 0	0 10	3 4	0 14	5 1	0 34	12 2	180
Low Control	782174	0.39	0 03	8 3	0 02	5 6	0 06	15.7	0 00	0 0	0 07	18 7	120
Low Control	783154	0.40	0 03	6 5	0 01	2 9	N/A	N/A	0 03	7 0	0 04	10 0	60
High Control	782174	2.86	0 19	6.5	0 11	4 0	0 15	5 3	0 00	0 0	0 27	9.3	120
High Control	783154	3.06	0 12	4 0	0 13	4 3	N/A	N/A	0 00	0 0	0 18	5 8	60

SD = standard
CV = coefficient of variation
N/A = Not applicable

[a] Variability of the assay performance from replicate to replicate

[b] Variability of the assay performance from day to day

[c] Variability of the assay performance from site to site

[d] Variability of the assay performance from reagent lot to reagent lot

[e] Variability of the assay performance combining the effect of all four components

Paired Matrix Study

Using patients from the prospective population, matched serum specimens, EDTA plasma specimens, and lithium heparin plasma specimens were collected (217 EDTA specimens, 217 lithium heparin specimens, and 218 serum specimens). There were no Index Values for 1 sample collected in lithium heparin and for another sample collected in EDTA. To ensure paired comparisons of control serum versus heparinized or EDTA-treated samples, it was necessary to use 1 additional serum specimen (i.e., 218 total samples instead of 217 samples). Serum and plasma were tested in replicates of 3 per sample type using the ADVIA Centaur® HBc Total assay and appropriate assay controls. Testing for all sample types and replicates for each specimen (i.e., individual) were performed in the same run. Samples collected in EDTA and lithium heparin were evaluated against serum (control) samples to determine matrix equivalency.

Samples collected with EDTA show 1.1 % bias when compared to serum, and samples collected with lithium heparin show 0.40% bias when compared to serum. Although comparisons of the mean control serum Index Value to the mean lithium heparin Index Value and the mean EDTA Index Value showed statistically significant differences they are not considered to be clinically significant. Results of the paired matrix study are summarized in the following table.

Bayer ADVIA Centaur® HBc Total Assay Matrix Study Summary (All Testing Sites)	
Specimen Type	**Mean ADVIA Centaur® HBc Total Index Value**
Serum (control)	2.65
EDTA plasma	2.63
Lithium heparin plasma	2.66
Difference in Mean ADVIA Centaur® HBc Total Index Value	
Control vs. EDTA	Control vs. Heparin
0.03 ($P = 0.0262$)[a]	-0.01 ($P = 0.1297$)[a]

a P value for the comparison of difference of Mean Serum Control Index versus Mean Heparin/Mean EDTA Index (2-sample comparison: t-Test or Wilcoxon Rand Test as appropriate after testing for normality).

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 Total assay:

Result Interpretation Using ADVIA Centaur® HBc Total assay		
ADVIA Centaur® HBc Total Assay Result	**Status**	**Interpretation**
<0.50	Nonreactive	Patient is assumed not to have an ongoing or previous HBV infection.
0.50 to 0.99	Retest range	Repeat in duplicates, two out of three results must fall > or< 0.5. Follow the interpretation accordingly.
≥0.50	Reactive	Patient is considered to have an ongoing or previous HBV infection.

Device Failures and Replacements

There were no apparent reported failures and/or replacements.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Multi-centered clinical studies were conducted in the US. The ADVIA Centaur® HBc Total assay method comparison was performed with 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 method and the reference assay was 93.21% (728/781) in the high risk, signs and symptoms, and dialysis populations combined. The overall negative percent agreement between the ADVIA Centaur® HBc Total method and the reference assay was 96.20% (1191/1235) in the high risk, signs and symptoms, and dialysis populations combined.

In the HBV infected acute and chronic retrospective population, the overall positive

percent agreement was 100.00% (153/153). None of the samples from the retrospective population were negative in the ADVIA Centaur® HBc Total method or in the reference assay.

The ability of the ADVIA Centaur® HBc Total assay to detect HBV infections was demonstrated with the seroconversion panel evaluation. When the ADVIA Centaur® HBc Total result was compared to the reference assay results, the first reactive time point for the ADVIA Centaur® HBc Total assay occurred earlier in 1 panel and at the same time in 6 panels.

Precision and reproducibility of the ADVIA Centaur® HBc Total assay was established for 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 Total assay.

The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur® HBc Total assay can be used safely and effectively for the qualitative in vitro determination of anti-HBc IgM and/or IgG in human serum and plasma. The ADVIA Centaur® HBc Total assay may be used with other HBV serological markers to define the clinical status of patients known to be infected with HBV or may be used with other HBV, HAV, and HCV assays to form a panel for the diagnosis of patients presenting with symptoms of viral hepatitis.

RISK BENEFIT ANALYSIS

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

The potential risks encountered with this *in vitro* diagnostic test are not unusual in the clinical laboratory setting. Appropriate warnings for these risks are contained in the labeling and package inserts for these devices. Standard good laboratory practices are considered sufficient to mitigate the risks to the end user.

SAFETY

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

EFFECTIVENESS

The effectiveness of the ADVIA Centaur® HBc Total has been demonstrated for use in determining if antibodies to the core antigen of the hepatitis B virus are present in an

individual's serum or plasma . A reasonable determination of effectiveness of the ADVIA Centaur® HBc Total assay for aiding in the diagnosis of acute and chronic 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 Advisory 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 December 22, 2004.

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

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.