SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Antibodies to Hepatitis B Core Antigen Assay

Device Trade Name: ADVIA Centaur® HBc Total 2 (HBcT2)
ADVIA Centaur® HBc Total 2 Quality Control (HBcT2 QC)
Atellica IM® HBc Total 2 (HBcT2)
Atellica IM® HBc Total 2 Quality Control (HBcT2 QC)

Device Procode: LOM

Applicant's Name and Address: Siemens Healthcare Diagnostics Inc
511 Benedict Ave
Tarrytown, NY 10591

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P210019/S002

Date of FDA Notice of Approval: April 28, 2023

The original PMA (P210019) was approved on July 27, 2022 and is indicated for ADVIA Centaur® HBc Total 2 (HBcT2) and Atellica IM® HBc Total 2 (HBcT2) on ADVIA Centaur XP/XPT and Atellica IM Analyzers in human adult serum and plasma (EDTA, lithium heparin, and sodium heparin) using ADVIA Centaur XP, ADVIA Centaur CPT, and Atelica IM. This assay can be used as an aid in the diagnosis of adults 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 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.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the

Inclusion of pediatric subjects in intended use population for the ADVIA Centaur® HBc Total 2 (HBcT2) on ADVIA Centaur XP/XPT, and ADVIA Centaur CP Analyzers, and Atellica IM® HBc Total 2 (HBcT2) on Atellica IM Analyzer.

II. INDICATIONS FOR USE

The ADVIA Centaur® HBc Total 2 (HBcT2):

The ADVIA Centaur® HBc Total 2 (HBcT2) assay is an in vitro diagnostic immunoassay for use in the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBV) in human pediatric (2-21 years old) and adult serum and plasma (EDTA, lithium heparin, and sodium heparin) using the ADVIA Centaur® XP and ADVIA Centaur® XPT systems.

This assay can be used as an aid in the diagnosis of 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 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.

This assay is not intended for screening donors of blood or blood products or human cells, tissues, and cellular and tissue-based products (HCT/Ps).

ADVIA Centaur® HBc Total 2 Quality Control (HBcT2 QC)

The ADVIA Centaur® HBc Total 2 (HBcT2) Quality Control material is for in vitro diagnostic use for monitoring the performance of the ADVIA Centaur HBc Total 2 (HBcT2) assay using the ADVIA Centaur systems.

The performance of the ADVIA Centaur HBcT2 Quality Control material has not been with any other anti-HBc Total assay.

The ADVIA Centaur® HBc Total 2 (HBcT2):

The ADVIA Centaur® HBc Total 2 (HBcT2) assay is an in vitro diagnostic immunoassay for use in the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBV) in human pediatric (2-21 years old) and adult serum and plasma (EDTA, lithium heparin, and sodium heparin) using the ADVIA Centaur® CP systems.

This assay can be used as an aid in the diagnosis of 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 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.

This assay is not intended for screening donors of blood or blood products or human cells, tissues, and cellular and tissue-based products (HCT/Ps).

ADVIA Centaur® HBc Total 2 Quality Control (HBcT2 QC)

The ADVIA Centaur® HBc Total 2 (HBcT2) Quality Control material is for in vitro diagnostic use for monitoring the performance of the ADVIA Centaur HBc Total 2 (HBcT2) assay using the ADVIA Centaur systems.

The performance of the ADVIA Centaur HBcT2 Quality Control material has not been with any other anti-HBc Total assay.

The Atellica IM HBc Total 2 (HBcT2):

The ADVIA Centaur® HBc Total 2 (HBcT2) assay is an in vitro diagnostic immunoassay for use in the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBV) in human pediatric (2-21 years old) and adult serum and plasma (EDTA, lithium heparin, and sodium heparin) using the Atellica IM Analyzer.

This assay can be used as an aid in the diagnosis of 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 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.

This assay is not intended for screening donors of blood or blood products or human cells, tissues, and cellular and tissue-based products (HCT/Ps).

Atellica IM® HBc Total 2 Quality Control (HBcT2 QC)
The Atellica IM HBc Total 2 (HBcT2) Quality Control material is for in vitro diagnostic use for monitoring the performance of the Atellica IM HBc Total 2 (HBcT2) assay using the Atellica IM systems.

The performance of the Atellica IM HBcT2 Quality Control material has not been with any other anti-HBc Total assay.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the device labeling.

V. DEVICE DESCRIPTION

There have been no changes to the device associated with the addition of pediatric populations to the intended use.

Assay Principle and Format

The ADVIA Centaur/Atellica Anti-HBcT2 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 and is used to capture anti-HBc in the patient sample.

The Lite Reagent contains recombinant HBc antigen labeled with acridinium ester and anti-human IgG Fab monoclonal antibody labeled with acridinium ester and is used to detect anti-HBc in the sample.

The Ancillary Reagent, Solid Phase, and Ancillary Well Reagent are added to the sample, followed by Lite Reagent. Antibody-antigen complexes will form if anti-HBc antibodies (IgM and IgG) are present in the sample.

A direct relationship exists between the amount of anti-HBc antibodies present in the patient sample and the amount of relative light units (RLUs) detected by the system. A result of reactive or nonreactive is determined according to the Index Value established with the calibrators.

Assay procedure:

The ADVIA Centaur system automatically performs the following actions:

1. Dispenses 50 µL of sample into a cuvette.
2. Dispenses 100 µL of Ancillary Reagent and incubates the mixture for 6 minutes at 37°C.
3. Dispenses 100 µL of Ancillary Well Reagent and 125 µL of Solid Phase, and incubates the mixture for 18 minutes at 37°C.
4. Washes the cuvette with ADVIA Centaur Wash 1.
5. Resuspends with 250 uL of ADVIA Centaur Wash 1 and incubates the mixture for 6 minutes at 37°C.
6. Dispenses 100 µL of Lite Reagent and incubates the mixture for 18 minutes at 37°C.
7. Washes the cuvette with ADVIA Centaur Wash 1.
8. Dispenses 300 µL of ADVIA Centaur Acid Reagent and 300 µL of ADVIA Centaur Base Reagent to initiate the chemiluminescent reaction.
9. Reports results.

The Atellica IM automatically performs the following actions:

1. Dispenses 50 µL of sample into a cuvette.
2. Dispenses 100 µL of Ancillary Reagent into a cuvette, then incubates for 6 minutes at 37°C.
3. Dispenses 100 µL of Ancillary Well Reagent and 125 µL of Solid Phase, then incubates for 18 minutes at 37°C.
4. Performs a wash sequence using Atellica IM Wash.
5. Resuspends the particles in 250 µL of Atellica IM Wash.
6. Dispenses 100 µL of Lite Reagent, then incubates for 18 minutes at 37°C.
7. Performs a wash sequence using Atellica IM Wash.
8. Dispenses 300 µL each of Atellica IM Acid and Atellica IM Base to initiate the chemiluminescent reaction.
9. Reports results.

Calibration

The ADVIA Centaur/Atellica Anti-HBcT2 assay utilizes two-point calibration (Low Calibrator, High Calibrator). The assay utilizes a factory-set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The Master Curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values on the system. The two calibrators in the kit are run when the lot is first used or after expiration of the calibration interval. If the calibration run is valid as determined by prearranged parameters, the values are stored and used to "normalize" test values to the Master Curve.

The Index value of the sample or control is read off the Master Curve. Individuals whose samples read at or above an Index of 1.0 are considered to be reactive for HBcT2.

Controls

The ADVIA Centaur HBcT2 QC and Atellica IM HBcT2 QC set contains Negative control (2 vials with 7 mL) and Positive control (2 vials with 7 mL). The performance of the ADVIA Centaur and Atellica IM HBcT2 assay is monitored by the use of ADVIA Centaur HBcT2 or Atellica IM HBcT2 QC Quality Controls at least once during each day when samples are analyzed or after a successful calibration.

Interpretation of Results

The system reports HBcT2 assay results in Index Values and as Nonreactive or Reactive:

• Nonreactive: < 1.0 Index. These samples are considered negative.

• Reactive: ≥ 1.0 Index. These samples are considered positive.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the determination of HBV infection and its disease stage. Detection of anti-HBcT in patients who may be infected with the hepatitis B virus may also be accomplished with any commercially available FDA approved serological tests. This assay is one of several hepatitis marker assays that are often used together and in conjunction with clinical assessment and other laboratory test results in the diagnosis of the HBV infection.

VII. MARKETING HISTORY

ADVIA Centaur HBc Total 2 (HBcT2) assay and ADVIA Centaur HBc Total 2 Quality Control (HBcT2 QC) are marketed globally in several countries. The device has not been withdrawn to date from the market in any country for reasons relating to safety and effectiveness of the device.

Austria	Belgium	Switzerland	Czech Republic
Germany	Denmark	Estonia	Spain
Finland	France	United Kingdom	Greece
Croatia	Hungary	Ireland	Iceland

Italy	Liechtenstein	Lithuania	Luxembourg
Latvia	North Macedonia	Malta	Netherlands
Norway	Poland	Romania	Serbia
Sweden	Slovenia	Slovakia	Afghanistan
Ukraine	United Arab Emirates	Cyprus	Hong Kong
India	Iraq	Turkey	Saudi Arabia
Singapore	Malaysia	Canada	Chile
Chile	Peru	South Africa	Zimbabwe
Madagascar	Bahrain	Pakistan	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects associated with the use of the device.

Failure of the product to perform as indicated, or human error in use of the product may lead to a false result. Repeatedly erroneous false positive or false negative anti-HBc results could lead to inappropriate initiation or cessation of antiviral therapy.

The risk of incorrect test results is inherent with all in vitro diagnostic products. Therefore, the above potential risks are not unusual in the laboratory setting and should be evaluated in conjunction with other clinical indicators.

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

IX. SUMMARY OF NONCLINICAL STUDIES

The non-clinical studies previously conducted (P210019) continue to be applicable to and supportive of the use of the device in pediatric populations. Siemens conducted additional laboratory studies (summarized below) to confirm continued performance of the device in pediatric populations.

A. Laboratory Studies

Precision

Precision study on ADVIA Centure Anti-HBcT2 assay on ADIVIA Centaur CP analyzer:

The ADVIA Centaur Anti-HBcT2 assay precision was examined in a 20-day precision protocol using one reagent lot. Two controls and 5 specimens in 2 matrices (serum and EDTA plasma) were used to measure the precision of the assay at different Index levels. The specimens were assayed in duplicate with 2 runs per day for 20 days (N = 80 for each sample). Table 1 below show the results of precision study

Table 1: ADVIA Centaur CP Precision study results

Specimen Type	N[a]	Mean	Repeatability		Within-Laboratory Precision	
			SD[b]	CV[c]	SD	CV[c]
		(Index)	(Index)	(%)	(Index)	(%)
Plasma A	80	0.21	0.02	N/A[d]	0.05	N/A
Plasma B	80	0.68	0.04	N/A	0.08	N/A
Plasma C	80	1.6	0.07	4.4	0.14	8.9
Plasma D	80	2.22	0.09	4.1	0.21	9.6
Plasma E	80	7.66	0.39	5.1	0.89	11.6
Serum A	80	0.13	0.02	N/A	0.06	N/A
Serum B	80	0.56	0.03	N/A	0.07	N/A
Serum C	80	1.49	0.07	4.4	0.15	10.3
Serum D	80	2.22	0.09	3.9	0.2	9
Serum E	80	6.71	0.36	5.3	0.68	10.1
Control 1 (negative)	80	0.21	0.02	N/A	0.06	N/A
Control 2 (positive)	80	3.12	0.13	4.2	0.27	8.5

[a]Number of measurements
[b]Standard deviation
[c]Coefficient of variation
[d]Samples recovering below 0.70 Index are not included in analysis

System Reproducibility

Reproducibility study of ADVIA Centure Anti-HBcT2 on ADIVIA Centaur CP analyzer:

A six-member panel, and QC1 and QC2 were assayed in triplicate for five days, two runs per day, at the three sites. The end of the first run on a testing day was separated from the start of the second run by approximately two hours. Each site ran three reagent lots with their respective calibrators and controls. The system reproducibility was determined in accordance with CLSI Document EP05-A3A reproducibility study was conducted at 3 sites, with each site evaluating 3 reagent lots. The protocol was run over 5 days, 2 runs per day. There were 3 replicates per run for each sample, for a total 270 replicates per sample (N = 270). Results were established using the ADVIA Centaur CP system. The following results are representative of the performance of the assay.

Table 2: ADVIA Centaur CP Reproducibility study across sites and reagent lots

Sample	Mean	Repeatability (Within-Run)		Between Run		Between Day		Between Lot		Within Laboratory		Between Site		Reproducibility	
Type		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
(N = 270)	Index	Index	%	Index	%	Index	%	Index	%	Index	%	Index	%	Index	%
Serum A	0.4	0.02	N/A[d]	0.02	N/ A	0.02	N/ A	0.06	N/A	0.04	N/A	0	N/ A	0.07	N/A
Serum B	0.71	0.03	N/A	0.03	N/ A	0.03	N/ A	0.06	N/A	0.05	N/A	0	N/ A	0.08	N/A

Serum C	1.34	0.05	3.6	0.04	2.8	0.04	2.8	0.12	8.8	0.07	5.3	0.02	1.5	0.14	10.4
Serum D	2.41	0.08	3.3	0.07	3.1	0.08	3.4	0.18	7.4	0.14	5.6	0.02	0.7	0.23	9.3
Serum E	5.28	0.22	4.1	0.19	3.6	0.16	3.1	0.36	6.8	0.33	6.2	0.12	2.2	0.5	9.5
Serum F	8.66	0.33	3.9	0.27	3.1	0.37	0.3	0.56	6.5	0.38	4.4	0.12	1.4	0.69	8
Control 1 (nega-tive)	0.19	0.02	N/A	0.02	N/ A	0.01	N/ A	0.03	N/A	0.04	N/A	0.02	N/ A	0.05	N/A
Control 2 (positive)	3.28	0.11	3.4	0.06	1.8	0.11	3.4	0.23	7.1	0.17	5.1	0.08	2.3	0.3	9.1

Sensitivity Study with HBV WHO First International Standard

The analytical sensitivity of the ADVIA Centaur/Atellica Anti-HBcT2 assay was evaluated using the World Health Organization (WHO) First International Standard for anti-Hepatitis B core antigen (anti-HBc).

The WHO Standard was reconstituted and diluted according to manufacturer's instructions. A stock solution of the standard was used to prepare a dilution series with negative human serum. The first level in the dilution series (A) was prepared by mixing 1 part of the NIBSC 95/522 50 IU/mL stock solution with 1 part of anti-HBc negative serum. The serial dilutions were then prepared by adding anti-HBc negative serum. Each diluted sample was tested in triplicate with the ADVIA Centaur/Atellica Anti-HBcT2 assay using an ADVIA Centaur XP, XPT, ADVIA Centaur CP and Atellica IM instrument. The observed dose was calculated using 2-point calibration. The quantitative value of WHO material detected at cutoff (Index = 1.00) was calculated using linear regression analysis. Analytical sensitivity evaluated with three different reagent lots of ADVIA Centaur/Atellica Anti-HBcT2 assay on ADVIA Centaur XP, XPT, ADVIA Centaur CP and Atellica IM instruments yield only minor differences from the WHO International Standard in all cases, as shown below in Table 3. The WHO 95/522 International Unit per milliliter (IU/mL) concentration at the assay cutoff was determined to be 0.28 IU/mL.

Table 3: Value of WHO material (IU/mL) detected at HBcT2 cutoff (Index = 1.00) and Correlation Coefficient

Reagent Lot	**Platform**							
	ADIVA Centaur XP		**ADVIA Centaur XPT**		**Atellica IM**		**ADVIA Centaur CP**	
	IU/mL	**R^2**	**IU/mL**	**R^2**	**IU/mL**	**R^2**	**IU/mL**	**R^2**
Lot 1	0.225	0.998	0.267	0.996	0.218	0.98	0.980	0.228
Lot 2	0.234	0.997	0.231	0.995	0.211	0.995	0.995	0.256
Lot 3	0.254	0.997	0.231	0.995	0.251	0.992	0.992	0.218

Seroconversion Sensitivity

Seroconversion study on ADVIA Centure Anti-HBcT2 assay on ADIVIA Centaur CP analyzer:

Commercially available HBV patient seroconversion panels were tested using the ADVIA Centaur Anti-HBcT2 to determine the seroconversion sensitivity of the assay on ADVIA Centaur CP analyzer.
The same 7 commericallly available HBV serocoversion panels used in the original PMA P210019 were tested at the same three US clinical sites. Each site tested at least 2 seroconversion panels. The following results were obtained with the ADVIA Centaur CP instrument:

Table 4: Seroconversion Resultson ADVIA Centaur CP HBcT2 versus Referenec assay

Panel ID	First HBcT2 Reactive Result From Initial Draw Date		ADVIA Centaur CP HBcT2 versus Reference Assay
	ADVIA Centaur CP Assay (Days)	Reference Assay (Days)	Difference in Bleed Numbers[a]
HBV6278	41	41	0
HBV6281	41	41	0
HBV9093	49	49	0
HBV9099	74	74	0
PHM941	99	99	0
SCPHBV1	29	29	0
SCPHBV4	65	71	+1

a 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 the ADVIA Centaur assay confirmed reactive.

Stability for Calibration interval for ADVIA Centaur CP system:

The stability of the working calibration curve was evaluated on the ADVIA Centaur CP instrument with two lots of ADVIA Centaur HBcT2. Reagents were placed on onboard ADVIA Centaur CP for the duration of the study. Testing was performed with calibrators (Low, High) and controls (Control 1, Control 2) run as samples and patient pools spiked with anti-HBc. All samples were tested in replicates of 4. In addition to testing open onboard reagents, fresh static packs were tested at each timepoint. The results support the calibration interval claim of 21 days on ADVIA Centaur CP instrument.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

Siemens performed a clinical study to establish a reasonable assurance of safety and effectiveness of the ADVIA Centaur/Atellica Anti-HBcT2 assay with samples from pediatric individuals. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A summary of the clinical study is presented below on ADVIA Centaur CP analyzer.

A. Study Design

A multisite study was conducted to evaluate the performance of the ADVIA Centaur/Atellica Anti-HBcT2 assay. The study consists of a Qualitative Method Comparison Agreement with a reference assay (FDA-approved Anti-HBcT assay).

Subjects were assessed for hepatitis markers using commercially available, FDA-approved reference assays. The serological assessment included the following 6 HBV markers: hepatitis B virus surface antigen (HBsAg), hepatitis B e antigen (HBeAg), IgM antibody to hepatitis B core antigen (anti-HBc IgM), total antibody to hepatitis B virus core antigen (anti-HBc Total), hepatitis B e antibody (anti-HBe , and antibody to hepatitis B virus surface antigen (anti-HBs).

Testing was conducted at three US sites with three reagent lots.

B. Accountability of PMA Cohort

A total of 1595 prospective subjects were enrolled for this study. The study population was considered either at risk for hepatitis B (due to lifestyle, behavior, occupation, or known exposure events) or had signs-and-symptoms of hepatitis B infection. Among 1595 specimens, 139 were from pediatric and non-pregnant adolescent subjects. The population analysis was stratified by the following age groups: 2-12 years (n=30) and 13-21 years (n=109).

C. Study Population Demographics and Baseline Parameters

Table 5. Pediatric subjects Demographics

Subject Demographics*		**Prospective Patient**	
		N	**(%)**
Characteristic	**Population**	139	100%
Category	Pediatric Patient	139	100%
Gender	Female	72	51.8%
	Male	67	48.2%
State of Residence	California	36	25.9%
	Florida	61	43.9%
	Minnesota	41	29.5%
	New Jersey	1	0.7%
Continent of Origin††	Africa	1	0.7%
	Asia	1	0.7%
	Caribbean	4	2.9%
	Central America	1	0.7%
	Mexico	2	1.4%
	North America	128	92.1%
	South America	2	1.4%

Ethnicity	Hispanic/Latino	21	15.1%
	Non-Hispanic/Non-Latino	118	84.9%
Race	White	30	21.6%
	Black or African American	92	66.2%
	Asian	6	4.3%
	Native Am/Alaska Native	2	1.4%
	multi-race	8	5.8%
	unknown/declined	1	0.7%
Age (Years)	Mean	16.9	
	Median	19	
	SD	4.8	
	Min	2	
	Max	21	
*Across sites;†† When subjects were asked to list their country of origin, there were 10 countries represented by the study population. The 10 countries were: Bahamas (1), Brazil (1), China (1), Colombia (1), Cuba (1), Haiti (2), Honduras (1), Mexico (2), Nigeria (1), United States (128).			

Percent Agreement on ADVIA Centaur CP analyzer:

ADVIA Centaur Anti-HBcT2 assay was tested on ADVIA Centaur CP system and the agreement calculated against an FDA-approved anti-HBcT reference assay. The Percent Positive Agreement (PPA) and Negative Percentage of Agreement (NPA) versus the reference assay on the different instrument systems is in Table 6.

Table 6:Agreement Table with ADVIA Centaur CP

ADVIA Centaur CP HBcT2	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	433	17	450
Nonreactive	10	1135	1145
Total	443	1152	1595

% Positive Agreement = 97.7% (433/443)
95% Confidence Interval = 95.9%–98.8%
% Negative Agreement = 98.5% (1135/1152)
95% Confidence Interval = 97.6%–99.1%

Expected Values

All of the samples from the 1595 unique patients including pregnant women were tested with the ADVIA Centaur/Atellica Anti-HBcT2.

See P210019 SSED for expected values in adults.
The below table 7 shows the expected values form pediatric population (2-21years old)

Table 7: Expected Values with ADVIA Centaur XP Pediatric population

Age Range (Years)	Reactive		Nonreactive		Total Number Tested
	N	%	N	%	
2-12	1	3.4%	29	96.7%	30
13-21	4	3.8%	105	96.3%	109
Total	5	3.7%	134	96.4%	139

D. Safety and Effectiveness Results

1. Safety Results

The safety of this device is related to the efficacy described below as incorrect results may lead to patient mismanagement.

2. Effectiveness Results

Prospective Population

The performance of the ADVIA Centaur Anti-HBcT2 assay was evaluated against the risk groups, the disease classification, and the subpopulations. The performance on the ADVIA Centaur CP analyzer is presented below:

By Risk Group

The performance of the ADVIA Centaur Anti-HBcT2 assay was evaluated in the signs and symptoms prospective populations and compared to the reference assay (Table 8). The percent agreement and confidence intervals for the prospective population by risk group is presented below (Table 9).

1) Signs and Symptom prospective population on ADVIA Centaur CP:

Table 8: ADVIA Centaur CP – Comparison of Results in the Signs and Symptoms Prospective Population

ADVIA Centaur HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	189	11	200
Nonreactive	5	571	576
Total	**194**	**582**	**776**

% Positive Agreement = 97.4% (189/194)
95% Confidence Interval = 94.1%–98.9%
% Negative Agreement = 98.1% (571/582)
95% Confidence Interval = 96.6%–98.9%

2) High-Risk Prospective Population:

Table 19: ADVIA Centaur CP – Comparison of Results in the High-Risk Prospective Population

ADVIA Centaur HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	**244**	**6**	**250**
Nonreactive	**5**	**564**	**569**
Total	**249**	**570**	**819**

Positive Percent Agreement: 98.0% (244/249)
95% Confidence Interval: 95.4%–99.1%
Negative Percent Agreement: 98.9% (564/570)
95% Confidence Interval: 97.7%–99.5%

a. By HBV Serological Classification

A total of 1595 samples including the 35 unclassified serostatus samples were evaluated using the ADVIA Centaur Anti-HBcT2 assay on ADVIA Centaur CP and an FDA approved reference Anti-HBcT assay for each sample classification. The agreement and 95% CIs between the ADVIA Centaur Anti-HBcT2 assay and a reference Anti-HBcT assay for each HBV classification are presented in the Table 10.

Below table 10 shows results on ADVIA Centaur CP systems

Table 10: Positive and Negative Percent Agreements Between ADVIA Centaur CP HBcT2 assay and reference Anti-HBcT assay by HBV Classification

ADVIA Centaur CP Percent Agreement with Reference Assay						
HBV Classification	**Positive Percent Agreement**			**Negative Percent Agreement**		
	(x/N)	**%**	**95% CI**	**(x/N)**	**%**	**95% CI**
Acute, N=3	(3/3)	100%	43.9-100%	NA	NA	NA
Chronic, N=77	(77/77)	100%	95.2-100%	NA	NA	NA
Early Recovery, N=15	(15/15)	100%	79.6-100%	NA	NA	NA
Recovered, N=223	(207/209)	99.0%	96.6-99.7%	(5/14)	35.7%	16.3-61.2%
Recovery, N=105	(101/101)	100%	96.3-100%	(3/4)	75.0%	30.1-95.4%
HBV Vaccine Response, N=539	(19/25)	76.0%	56.6-88.5%	(511/514)	99.4%	98.3-99.8%
Not Previously Infected, N=599	(3/5)	60.0%	23.1-88.2%	(591/594)	99.5%	98.5-99.8%
Unclassified, N=34	(8/8)	100%	67.6-100%	(25/26)	96.2%	81.1-99.3%
Total, N=1595	(433/443)	97.7%	95.9–98.8%	(1135/1152)	98.5%	97.6-99.1%

b. Pediatric population

Pediatric and adolescent (non-pregnant) samples were prospectively collected (N = 139) and tested using the ADVIA Centaur XP system. The population analysis was stratified by the following age groups: 2–12 years and 13–21 years. Results of

the testing (reactive and nonreactive) were compared using the ADVIA Centaur HBcT2 assay and the reference anti-HBcT assay for pediatric population.

Table 11: Percent Agreement and Confidence Intervals: Pediatric Populations

Age Range (Years)	Positive Percent Agreement		Negative Percent Agreement	
	% (x/n)	95% Confidence Interval	% (x/n)	95% CI
2–12	100 (1/1)	20.7–100	100 (29/29)	88.3–100
13–21	100 (3/3)	43.9–100	99.1 (105/106)	94.8–99.8
Total	**100 (4/4)**	**51.0–100**	**99.3 (134/135)**	**95.9–99.9**

Because few positives were identified (4/139) in pediatric population study, a spiking study was conducted to evaluate the results, when pediatric samples are tested with the ADVIA Centaur HBcT2 assay using the ADVIA Centaur XP system. A total of 60 pediatric (age 2–21 years) and 60 adult serum samples were spiked with unique native anti- HBc positive samples. The mean percent bias between each paired spiked pediatric donor samples versus spiked adult donor samples was analyzed.

Out of 60 pediatric samples tested 59 samples showed bias less than 20% (98.3% samples). The distribution of percent bias between the Index values of the spiked pediatric serum samples and the paired adult serum samples are summarized in table 12.

Table 12:Distribution of percent bias in pediatric sample spiking study

Age Range (Years)	Distribution of Percent Bias			
	Na	≤ 10%	> 10%– ≤ 20%	> 20%– ≤ 30%
2–12	20	45.0 (9/20)	50.0 (10/20)	5.0 (1/20)
13–21	40	72.5 (29/40)	27.5 (11/40)	0.0 (0/40)
Total	60	63.3 (38/60)	35.0 (21/60)	1.7 (1/60)

c. Pregnant Population

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The

pivotal clinical study included 5 investigators of which 1 was a full-time or part-time employee of the sponsor and none had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the ADVIA Centaur/Atellica Anti-HBcT2 assay has been demonstrated by the sensitivity and specificity which has been comparable with the current commercially available FDA-approved anti-HBcT assays among all populations tested. The results from both the nonclinical and clinical studies indicate that the ADVIA Centaur/Atellica Anti-HBcT2 assay is safe and effective for the in vitro qualitative detection of total antibodies to the hepatitis B core antigen (Anti-HBc) in serum and plasma (EDTA, lithium heparin, and sodium heparin) collected from pediatric (age 2-21) and adult population.

B. Safety Conclusions

The risk of the device is based on data collected in the non-clinical and clinical studies conducted to support PMA approval as described above. Based on the results from both studies, the ADVIA Centaur/Atellica Anti-HBcT2 assay, when used according to the provided directions and in conjunction with all relevant clinical and laboratory findings, should be safe to use and poses minimal risk to the patient due to false test results.

C. Benefit-Risk Determination

The benefits of the assay are 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 HBV disease associated with HBV infection, and as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

Test results can facilitate initiation of appropriate monitoring, antiviral medications, and improved patient knowledge regarding the Hepatitis B infection. Treatment for appropriate patients can mitigate the sequelae of hepatitis B infection and may result in improved morbidity and mortality in these patients. Additionally, diagnosis and appropriate treatment can potentially decrease transmission and disease burden in the general population as well as in populations at high risk for hepatitis B infection.

Accurate diagnosis of HBV infection also leads clinicians to evaluate and subsequently treat patients for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) if
indicated as these viruses share common risk factors and modes of transmission with HBV, and patients are often coinfected.

The risks associated with the device, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results and failure to correctly operate the instrument.

Risks of false positive tests includes improper patient management, including treatment for hepatitis B with antiviral medication. Antiviral medical has risks including toxicity and more rarely allergic reactions. Over time, viral resistance in patients who are co-infected but undiagnosed with other viruses using the same antiviral medication, such as HIV, can lead to viral resistance, however the chance of an undiagnosed co-infection in a patient tested for hepatitis B is exceedingly unlikely. These risks are somewhat mitigated by the fact that this test is generally sent as part of a panel, and incongruous test results in a hepatitis panel would lead a clinician to retest the patient before starting treatment.

Risks of false negative tests include potentially missing the opportunity to treat a patient who has hepatitis B infection and whose clinical picture warrants antiviral treatment. A clinician may falsely believe that a patient is not acutely or chronically infected, but rather is currently susceptible or immune to the infection. False negative results may lead a clinician to vaccinate an infected patient. This risk is somewhat mitigated by the fact that this test is usually ordered as part of a panel of hepatitis B tests, and incongruous test results in a hepatitis panel would lead a clinician to retest the patient.

1. Patient Perspective

   Patient perspectives considered during the review included:

This submission either did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBV) in human pediatric (age 2-21 years) and adult serum and plasma, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity, precision, and analytical specificity of the ADVIA Centaur/Atellica Anti-HBcT2 assay when used according to the instructions for use as stated in the labeling, the warnings, and precautions, and limitations sections of the labeling. The clinical studies have shown that the ADVIA Centaur/Atellica Anti-HBcT2 assay, when compared to the FDA approved comparator, has a similar ability to detect the presence of anti-HBcT antibodies in specimens from individuals with chronic hepatitis B, or those recovered from HBV infection. The assay has also demonstrated that it has no cross-reactivity with viral antibodies or other cross-reactants in the specimens from individuals with medical conditions unrelated to the HBV infection. The probable clinical benefits outweigh the potential risks for the proposed assay considering the performance of the device in the clinical trial and the low risk and associated risk mitigations in clinical practice. The proposed assay labelling will facilitate accurate assay implementation and interpretation of results. The assay may provide substantial benefits to patients as an accurate and sensitive aid in determining HBV seroconversion in conjunction with other diagnostic information

XIII. CDRH DECISION

CDRH issued an approval order on.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.