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 of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P210019

Date of FDA Notice of Approval: July 27, 2022

II. INDICATIONS FOR USE

ADVIA Centaur® HBc Total 2 (HBcT2) assay
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 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 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.

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.

Atellica IM® HBc Total 2 (HBcT2) assay

The Atellica IM 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 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 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.

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

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

Cut-off Determination

The ADVIA Centaur/Atellica Anti-HBcT2 assay is a qualitative assay to detect human IgG and IgM antibodies against the core antigen of the Hepatitis B virus. The ADVIA Centaur/Atellica Anti-HBcT2 assay results are reported as Nonreactive or Reactive with 'Index' units. An Index value of ≥ 1.00 indicates the presence of anti-HBc antibodies in a sample, whereas, an Index value <1.00 indicates that the sample is negative for anti-HBc antibodies.

Internal master curve standards were made with increasing concentrations of anti-HBc antibodies in the feasibility phase of development. Each of the standard levels was assigned an Index value such that the resulting dose – response curve (RLU vs. Index) was used to calculate the concentration (Index units) of anti-HBc antibodies in samples. The assignment of the master curve standards was done such that a preliminary assay cut off was established at 1.00 Index while maintaining a separation between anti-HBc antibody positive and negative samples. This was done by evaluating known positive and negative samples, as determined by the HBcT2 index value, during the development of this assay via a qualitative method comparison to the HBcT2 assay which was used as the initial predicate device for research purposes.

During the development and verification phase of this assay development project, population studies were conducted with the reagent lots to further optimize the cutoff. The HBcT2 interpretation of samples that were discordant based on vendor Certificates of Analysis (CoA) was compared to an FDA-approved Anti-HBc II assay. Based on this data, the assignment of the master curve standards and calibrators were linearly adjusted and validated.

Precision

The ADVIA Centaur/Atellica Anti-HBcT2 assay precision in various sample matrices was examined in a 20-day precision protocol using 3 lots of reagent. 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).

The results in the following table are from one lot. Calculations for within-run, between-run, between-day, and total precision were performed according to Clinical and Laboratory Standards Institute (CLSI) Document EP05-A3.

Table 1: ADVIA Centaur Precision

			Repeatability		Within-Laboratory Precision	
Specimen Type	N[a]	Mean (Index	SD[b] (Index	CV[c] %	SD (Index	CV %
Plasma 1	80	0.39	0.02	N/A[d]	0.09	N/A
Plasma 2	80	0.78	0.03	N/A	0.06	N/A
Plasma 3	80	1.56	0.07	4.6	0.10	6.7
Plasma 4	80	2.38	0.11	4.5	0.15	6.3
Plasma 5	80	6.71	0.33	4.9	0.64	9.6
Serum 1	80	0.30	0.02	N/A	0.09	N/A
Serum 2	80	0.63	0.04	N/A	0.06	N/A
Serum 3	80	1.53	0.09	5.8	0.10	6.4
Serum 4	80	2.30	0.09	4.0	0.16	7.1
Serum 5	80	6.13	0.34	5.6	0.57	9.3
Control 1 (negative)	80	0.31	0.02	N/A	0.08	N/A
Control 2 positive	80	3.49	0.18	5.2	0.25	7.2

[a]Number of measurements
[b]Standard deviation
[c]Coefficient of variation
[d]Not applicable. Results remained nonreactive throughout the study

Table 2: Atellica IM Precision

			Repeatability		Within-Laboratory Precision	
Specimen Type	N[a]	Mean (Index	SD[b] (Index	CV[c] %	SD (Index	CV %
Plasma 1	75[d]	0.13	0.03	N/A[e]	0.03	N/A
Plasma 2	80	0.62	0.04	N/A	0.04	N/A
Plasma 3	80	1.38	0.06	4.3	0.06	4.3

Plasma 4	80	2.25	0.06	2.7	0.06	2.7
Plasma 5						3.7
Serum 1	77	0.10	0.03	N/A	0.05	N/A
Serum 2	80	0.46	0.04	N/A	0.07	N/A
Serum 3	80	1.41	0.07	4.8	0.12	8.3
Serum 4	80	2.17	0.10	4.4	0.16	7.2
Serum 5	80	5.73	0.27	4.7	0.39	6.8
Control 1 (negative)	80	0.24	0.02	N/A	0.04	N/A
Control 2 positive	80	3.52	0.10	2.9	0.14	3.9

[a]Number of measurements
[b]Standard deviation
[c]Coefficient of variation
[d]Samples recovering below 0.70 Index are not included in analysis
[e]Not applicable. Results remained nonreactive throughout the study

System Reproducibility

The system reproducibility of the ADVIA Centaur/Atellica Anti-HBcT2 assay was evaluated on ADVIA Centaur XP, XPT and the Atellica IM systems at two external US sites and one internal sponsor site within the US. A six-member panel, QC and calibrators 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-A3 The results obtained with the ADVIA Centaur XP, XPT, and Atellica IM are summarized below in the following tables.

Table 3: ADVIA Centaur XP Reproducibility Across Sites and Reagent Lots

			Repeatability		Run		Day		Lot		Within-Lab		Site		Reproducibility	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
High Calibrator	270	2.01	0.08	3.8%	0.05	2.5%	0.00	0.0%	0.06	2.9%	0.09	4.6%	0.15	7.6%	0.19	9.4%
Low Calibrator	270	0.61	0.03	5.6%	0.02	4.0%	0.01	1.5%	0.00	0.0%	0.04	7.0%	0.06	9.6%	0.07	11.9%
Negative Control	270	0.25	0.02	6.9%	0.03	12.7%	0.00	0.0%	0.02	8.3%	0.04	14.4%	0.03	13.5%	0.05	21.4%
Positive Control	270	3.28	0.14	4.3%	0.09	2.8%	0.00	0.0%	0.18	5.4%	0.17	5.1%	0.25	7.7%	0.35	10.7%
Serum 1	270	0.50	0.03	5.6%	0.03	6.3%	0.00	0.0%	0.01	2.9%	0.04	8.4%	0.03	5.5%	0.05	10.4%
Serum 2	270	0.83	0.03	4.2%	0.03	3.9%	0.00	0.0%	0.03	4.2%	0.05	5.7%	0.06	7.2%	0.08	10.1%
Serum 3	270	1.47	0.06	4.0%	0.02	1.7%	0.02	1.5%	0.12	7.9%	0.07	4.6%	0.11	7.2%	0.17	11.7%
Serum 4	270	2.56	0.11	4.4%	0.04	1.7%	0.03	1.2%	0.21	8.3%	0.12	4.9%	0.19	7.5%	0.31	12.2%
Serum 5	270	5.48	0.26	4.7%	0.06	1.2%	0.07	1.3%	0.48	8.8%	0.28	5.1%	0.40	7.3%	0.68	12.5%
Serum 6	270	8.71	0.38	4.4%	0.16	1.8%	0.00	0.0%	0.66	7.6%	0.41	4.7%	0.61	7.0%	0.98	11.3%

Table 4: ADVIA Centaur XPT Reproducibility Across Sites and Reagent Lots

			Repeatability		Run		Day		Lot		Within-Lab		Site		Reproducibility	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
High Calibrator	270	1.96	0.09	4.4%	0.05	2.6%	0.00	0.0%	0.16	8.2%	0.10	5.1%	0.10	5.2%	0.21	11.0%
Low Calibrator	270	0.57	0.03	5.4%	0.03	4.8%	0.00	0.0%	0.05	9.4%	0.04	7.3%	0.04	6.5%	0.08	13.5%
Negative Control	270	0.20	0.02	11.6%	0.02	8.3%	0.01	4.5%	0.06	29.5%	0.03	14.9%	0.02	12.1%	0.07	35.2%
Positive Control	270	3.21	0.14	4.2%	0.08	2.6%	0.00	0.0%	0.19	5.8%	0.16	5.0%	0.17	5.2%	0.30	9.2%
Serum 1	270	0.45	0.03	6.4%	0.01	3.0%	0.00	0.0%	0.07	16.4%	0.03	7.1%	0.02	3.4%	0.08	18.1%
Serum 2	270	0.79	0.03	3.8%	0.02	3.2%	0.00	0.0%	0.10	12.7%	0.04	5.0%	0.03	4.4%	0.11	14.3%
Serum 3	270	1.42	0.06	4.1%	0.03	1.9%	0.00	0.0%	0.18	12.6%	0.07	4.6%	0.06	4.4%	0.20	14.1%
Serum 4	270	2.50	0.10	3.9%	0.04	1.8%	0.00	0.0%	0.29	11.5%	0.11	4.3%	0.12	4.7%	0.33	13.1%
Serum 5	270	5.36	0.25	4.7%	0.08	1.5%	0.00	0.0%	0.63	11.8%	0.26	4.9%	0.26	4.8%	0.73	13.7%
Serum 6	270	8.48	0.37	4.3%	0.05	0.6%	0.06	0.7%	0.81	9.6%	0.38	4.4%	0.48	5.6%	1.01	11.9%

Table 5: Atellica IM Reproducibility Across Sites and Reagent Lots

			Repeatability		Run		Day		Lot		Within-Lab		Site		Reproducibility	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
High Calibrator	270	2.04	0.04	1.9%	0.03	1.5%	0.02	0.7%	0.02	1.2%	0.05	2.5%	0.02	1.1%	0.06	3.0%
Low Calibrator	270	0.63	0.02	2.9%	0.01	2.0%	0.01	2.3%	0.02	3.6%	0.03	4.2%	0.00	0.0%	0.03	5.5%
Negative Control	270	0.21	0.02	7.6%	0.01	5.3%	0.02	8.1%	0.06	30.1%	0.03	12.3%	0.01	6.0%	0.07	33.1%
Positive Control	270	3.29	0.07	2.1%	0.05	1.5%	0.03	0.8%	0.23	7.0%	0.09	2.7%	0.04	1.1%	0.25	7.6%
Serum 1	270	0.41	0.02	4.6%	0.02	3.7%	0.00	0.0%	0.09	21.2%	0.02	5.8%	0.00	0.0%	0.09	22.0%
Serum 2	270	0.76	0.02	2.7%	0.01	1.5%	0.01	1.7%	0.07	9.0%	0.03	3.4%	0.01	0.9%	0.07	9.7%
Serum 3	270	1.35	0.04	2.6%	0.01	0.6%	0.02	1.2%	0.13	9.5%	0.04	3.0%	0.00	0.0%	0.13	10.0%
Serum 4	270	2.40	0.06	2.4%	0.03	1.4%	0.02	1.0%	0.20	8.4%	0.07	3.0%	0.00	0.2%	0.21	8.9%
Serum 5	270	5.09	0.17	3.4%	0.12	2.4%	0.06	1.2%	0.41	8.1%	0.22	4.3%	0.00	0.0%	0.47	9.1%
Serum 6	270	8.38	0.21	2.6%	0.00	0.0%	0.09	1.1%	0.43	5.2%	0.23	2.8%	0.07	0.8%	0.50	5.9%

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, 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, and Atellica IM instruments yield only minor differences from the WHO International Standard in all cases, as shown below in Table 6. The WHO 95/522 International Unit per milliliter (IU/mL) concentration at the assay cutoff was determined to be 0.28 IU/mL.

Table 6: 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	
	IU/mL	R^2	IU/mL	R^2	IU/mL	R^2
136991	0.225	0.998	0.267	0.996	0.218	0.980
136990	0.234	0.997	0.231	0.995	0.211	0.995
136987	0.254	0.997	0.231	0.995	0.251	0.992

Seroconversion Sensitivity

Commercially available HBV patient seroconversion panels were tested using the ADVIA Centaur/Atellica Anti-HBcT2 assay to determine the seroconversion sensitivity of the assay. The performance of the ADVIA Centaur/Atellica Anti-HBcT2 assay on the seroconversion panels matched the performance of the reference assay. The following results were obtained with the ADVIA Centaur XP instrument:

Table 7: Seroconversion Sensitivity

Panel ID	**Reference Anti-HBc Total Assay - Reactive From Initial Draw Date**		**ADVIA Centaur HBcT2 Assay versus Reference Anti-HBc Total Assay**
	ADVIA Centaur HBcT2 Assay (Days)	**Reference Assay (Days)**	**Difference in Bleed Numbers[a]**
HBV6278			0
HBV6281	41	41	0
			0

HBV9099	74	74	0
			0
SCPHBV1	29	29	0
			+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.

Cross-Reactivity

The ADVIA Centaur/Atellica Anti-HBcT2 assay was evaluated for potential cross-reactivity with viral antibodies and disease state specimens. The anti-HBcT serostatus of each specimen was verified using an FDA approved reference assay. The following results were obtained using the ADVIA Centaur XP instrument:

Table 8: Cross-Reactivity

Substance	**Number Tested**	**Number of Reactive Anti-HBc Total Results**	
		ADVIA Centaur HBcT2 Assay	**Reference Assay**
Anti-nuclear antibody (ANA)			2
Cytomegalovirus (CMV) IgG	15	0	0
Cytomegalovirus (CMV) IgM			0
Epstein-Barr virus (EBV) IgG	15	0	0
Epstein-Barr virus (EBV) IgM			0
Flu vaccine recipient	15	0	0
Human anti-mouse antibody (HAMA)			2
Hepatitis A infection (HAV)	20	4	4
Hepatitis C infection (HCV)			7
Herpes simplex virus (HSV) IgG	15	0	0
Herpes simplex virus (HSV) IgM			0
Human immunodeficiency virus (HIV 1/2)	15	6	6
Multiparity			1
Non-viral liver disease	15	1	0
Rheumatoid arthritis			1
Rubella IgG	15	0	0
Syphilis IgG	15	3	3
Systemic lupus erythematosus (SLE)	20	1	1
Toxoplasma IgG	21	0	0

Toxoplasma IgM	11	0	0
Varicella zoster virus (VZV) IgG	15	1	1

Interference with Endongeneous Substances

The sensitivity of the ADVIA Centaur/Atellica Anti-HBcT2 assay to interference by endogenous substances was evaluated at the concentrations indicated in Table 9. Samples from 4 matrixes (serum, K2 EDTA, Li heparin, Na heparin) were tested on the ADVIA Centaur XP. Samples were made from pools of patient units with anti-HBc positive pool spiked or without (negatives). Two spiked samples were low positives (target index of 1.5-2.5) and intermediate positives (target index of >3.0), respectively. None of the evaluated endogenous substances resulted a change of the test result.

Table 9: Summary of Endogenous Substances used in the Interference Study

Substance	**Substance Test Concentration Units**
Hemolyzed	500 mg/dL
Icteric	60 mg/dL
Icteric	40 mg/dL
Lipemic	1000 mg/dL
Hyperproteinemic	12.0 g/dL
Hypoproteinemic	3.5 g/dL
Hyper IgG	60 mg/mL
Biotin	3500 ng/mL
Cholesterol	500 mg/dL

Specimen Matrix Equivalency

The study was performed on the ADVIA Centaur XP instrument to assess the influence of different matrices on the results of the ADVIA Centaur/Atellica Anti-HBcT2 assay. A total of 50 nonreactive matched sets were collected in five different blood collection tubes (Serum Glass, SST, K2 EDTA, Li Hep, and Na Hep). 10 matched sets were used to compare nonreactive blood collective tubes versus serum glass while 40 matched sets were separated and spiked with 1 unique reactive positive serum sample per matched set to 4 different target levels in order to span the assay Index range of 0.07 – 10.00 Index. The target ranges were 0.75 Index (High Negative), 1.50 Index (Low Positive), 2.50 Index (Moderate Positive), and 3.00 – 10.00 Index (High Positive) respectively. Samples were tested on one ADVIA Centaur XP instrument using one reagent lot. Data were analyzed by Deming regression and results for each tube type were compared to the results of serum glass.

The results for all matrices were plotted on a XY graph compared to the values obtained from serum samples and weighted Deming regression fit was used to evaluate the variability. The correlation coefficient was calculated using Pearson correlation. Matrix equivalency was determined in accordance with CLSI Document EP09-A3, *Measurement Procedure*

Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition. All samples demonstrated acceptable assay equivalency between matrices throughout the measurement range (Table 10).

Table 10: Regression Statistics for ADVIA Centaur HBcT2 Matrix Comparisons

Tubes Types	Slope	Intercept	r
SST vs Serum Glass	0.960	0.043	98.3%
K2 EDTA vs Serum Glass	0.979	0.025	98.1%
Li Heparin vs Serum Glass	1.000	-0.053	96.8%
Na Heparin vs Serum Glass	1.042	-0.093	97.1%

Stability Studies

a. Specimen Stability

Studies were performed to determine the stability of patient samples under different storage conditions. Specimens were collected in the following tube types: serum glass tubes, serum separator tubes (SST), K2EDTA plasma tubes, sodium heparin plasma tubes, and lithium heparin plasma tubes. The effect of multiple freeze/thaw cycles, time to centrifugation, and onboard storage on the stability of the samples was also evaluated.

A minimum of ten samples were used for each sample handling with samples spanning the assay range including:

- <1.00 Index (Non-reactive samples)
- 1.00-3.00 Index (Low Reactive)
- >3.00 Index

Nonreactive anti-HBc samples were spiked with anti-HBc Reactive samples in order to achieve the desired sample distribution.

Samples were aliquoted and placed in the appropriate storage/stress conditions. A baseline Index value, t0, was established for each sample. For reactive samples bias ± 15% of t0 was determined by trend analysis. Non-reactive samples remained non-reactive.

Additionally, samples stored frozen were subjected to 6 freeze-thaw cycles. Bias lower than ±15% versus t0 were observed.

The results of the sample handling and storage temperature studies, freeze/thaw, and frozen (-20°C) studies support the claims for stability for all samples and matrices (serum or SST, EDTA plasma and Lithium Heparin plasma) (Table 11).

Table 11: Summary of the Results for the Sample Stability Study Types

Storage Condition	Claimed Stability
Time to Centrifugation	24 hours
Primary Tube Storage	7 Days
Onboard Storage	24 hours
Room Temp Storage (25º C)	3 Days

Refrigerated Storage (2-8º C)	7 Days
Frozen Storage (-20º C)	12 Months
Freeze/Thaw Cycles	5

b. Reagent Stability

Reagent Real Time Stability Study (Shelf-Life)

Real time stability testing was performed on three lots of ADVIA Centaur Anti-HBcT2 on the ADVIA Centaur XP instrument and three lots of Atellica IM HBcT2 on the Atellica IM instrument to determine reagent shelf-life when stored at 2–8°C. Each lot was stored at 2–8°C and was tested at pre-determined checkpoints from T = 0 to 108 weeks (ADVIA Centaur Anti-HBe2) or 124-138 weeks (Atellica Anti-HBe2). The results support the shelf-life claim of 24 months for ADVIA Centaur and Atellica IM HBcT2 assay stored at 2–8°C.

Stability of the Calibration Interval

The stability of the working calibration curve was evaluated on the ADVIA Centaur XP, XPT and Atellica IM instruments with two lots of ADVIA Centaur HBe2 and two lots of Atellica HBcT2. Reagents were placed on onboard ADVIA Centaur XP and Atellica IM 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 (ADVIA Centaur) or replicates of 3 (Atellica IM). 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 XP and XPT instruments and 42 days on the Atellica IM.

Calibrator Open Vial Stability

The study was performed with one lot of the ADVIA Centaur Anti-HBcT2 on the ADVIA Centaur XP instrument to establish the open vial stability at 2–8°C of calibrators versus the unopened vials. At each of the scheduled timepoints, a set of calibrators were assayed. Calibration for this study used a stored 2-point curve, based upon the calibration of the zero timepoint. Data was calculated from the 2-point calibration using calibrators held -40°C.

After the use of calibrator and controls, vials were returned to refrigerated storage until testing at the next time point. Materials were tested at multiple timepoints and were compared to Time 0. The results support the open vial stability claim of 70 days for ADVIA Centaur Anti-HBe2 Calibrators.

A similar study was conducted to determine how long an open vial of the Atellica IM HBcT2 Calibrators can remain on the Sample Handler of the Atellica IM Analyzer and provide acceptable results. The results of that study support the open vial stability claim up to 25 hours on the sample handler.

Calibrator On-Board Stability

ADVIA Centaur HBcT2 calibrators were tested on ADVIA Centaur XP over the course of 9 hours. The same study was conducted with Atellica HBcT2 calibrators tested on an Atellica IM instrument. At each of the scheduled timepoints, a set of calibrators were assayed. Calibration for this study used a stored 2-point curve, based upon the calibration of the zero

timepoint. Data was calculated from the 2-point calibration using calibrators held at -40°C. When Calibrators were run as samples, all results met the acceptance criteria up to 9 hours. The results support the on-board stability claim of 9 hours for the ADVIA Centaur Anti-HBcT2 Calibrators on the ADVIA Centaur XP and XPT instruments and Atellica Anti-HBcT2 Calibrators on the Atellica IM instrument.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

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

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. Study Population Demographics and Baseline Parameters

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. Table 12 summarizes the patient population demographics:

Table 12: Subject Demographics

Subject Demographics			
		N	(%)
Characteristic	**Population**	1595	100.0%
Category	Dialysis Patient	105	6.6%
	High Risk Patient	619	38.8%
	Hepatitis B	628	39.4%
	Pregnant Patient	193	12.1%
	Transplant Recipient	50	3.1%
Gender	Female	837	52.5%
	Male	758	47.5%

Subject Demographics			
		N	(%)
	Unknown	0	0.0%
State of Residence	Arizona	1	0.1
	California	436	27.2
	Florida	582	36.5
	Massachusetts	1	0.1
	Michigan	5	0.3
	Minnesota	533	33.6
	North Dakota	1	0.1
	Nevada	1	0.1
	Texas	2	0.1
	Virginia	1	0.1
	Wisconsin	1	0.1
	Other	31	1.9
	Africa	26	1.6
Continent of Origin	Asia	36	2.2
	Caribbean	116	7.3
	Central America	21	1.3
	Europe	7	0.4
	North America	1361	85.4
	South America	27	1.7
	South Pacific	1	0.1
Ethnicity	Non-Hispanic/Non-Latino	1345	84.3
	Hispanic/Latino	250	15.7
Race	White	483	30.3
	Black or African American	973	61.0
	Asian	39	2.4
	Native Am/Alaska Native	54	3.4
	Native HI/Pacific Islander	6	0.4
	Other	9	0.6
	multi-race	23	1.4
	unknown/declined	8	0.5
Age (Years)	Mean	47.13	
	Median	50.0	
	SD	13.997	
	Min	21.0	
	Max	85.0	

Percent Agreement:

ADVIA Centaur/Atellica IM Anti-HBe2 assay was tested on all three platforms, ADVIA Centaur XP, XPT and Atellica IM systems and the agreement calculated against an FDA-approved aHBcT reference assay. An overview of the detailed results in the following

tables of the Percent Positive Agreement (PPA) and Negative Percentage of Agreement (NPA) versus the reference assay on the different instrument systems is below (Tables 13 - 15).

Table 13: Agreement Table with ADVIA Centaur XP

ADVIA Centaur XP HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	434	19	453
Nonreactive	9	1133	1142
Total	443	1152	1595

% Positive Agreement = 98.0% (434/443)
95% Confidence Interval = 96.2%–98.9%
% Negative Agreement = 98.4% (1133/1152)
95% Confidence Interval = 97.4%–98.9%

Table 14: Agreement Table with ADVIA Centaur XPT

ADVIA Centaur XPT HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	435	22	457
Nonreactive	8	1130	1138
Total	443	1152	1595

% Positive Agreement = 98.2% (435/443)
95% Confidence Interval = 96.5%–99.1%
% Negative Agreement = 98.1% (1130/1152)
95% Confidence Interval = 97.1%–98.7%

Table 15:Agreement Table with Atellica IM

Atellica IM HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	433	16	449
Nonreactive	10	1136	1146
Total	443	1152	1595

% Positive Agreement = 97.7% (433/443)
95% Confidence Interval = 95.9%–98.8%
% Negative Agreement = 98.6% (1136/1152)
95% Confidence Interval = 97.8%–99.1%

HBV Disease Classification:

Patients were assessed for hepatitis markers using commercially available, FDA-approved reference assays. Each patient's HBV infection status was determined based on the reactive (+) / nonreactive (-) patterns of six HBV reference serological markers obtained from a single specimen (Table 16): hepatitis B virus surface antigen (HBsAg), hepatitis B virus e antigen (HBeAg), total antibody to hepatitis B virus core antigen (anti-HBc Total), IgM

antibody to hepatitis B core antigen (anti-HBc IgM), total antibody to HBeAg (anti-HBe), and total antibody to hepatitis B virus surface antigen (anti-HBs).

There were 30 unique reference marker patterns observed using the FDA-approved assays (Table 16).

Table 16: Interpretation of hepatitis B Serologic Test Results used for Classifications

HBV Classification (n)	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc Total	Anti-HBe	Anti-HBs (> 10 mIU/mL)
Acute (1)	+	+	+	+	+	-
Acute (2)	+	+	+	+	-	-
Chronic (3)	+	+	-	+	+	-
Chronic (19)	+	+	-	+	-	-
Chronic (49)	+	-	-	+	+	-
Chronic (1)	+	-	-	+	-	+
Chronic (5)	+	-	-	+	-	-
Early Recovery (4)	-	-	+	+	+	+
Early Recovery (2)	-	-	+	+	-	+
Early Recovery (9)	-	-	-	+	+	-
Recovery (102)	-	-	-	+	+	+
Recovery (3)	-	-	-	-	+	+
Recovered (156)	-	-	-	+	-	+
Recovered (67)	-	-	-	+	-	-
HBV Vaccine Response (539)	-	-	-	-	-	+
Not Previously Infected (599)	-	-	-	-	-	-
Unclassified (2)	+	-	-	-	-	+
Unclassified (2)	+	-	-	-	-	-
Unclassified (5)	-	+	-	-	-	+
Unclassified (9)	-	+	-	-	-	-
Unclassified (2)	-	-	+	-	-	-
Unclassified (2)	-	-	-	-	+	-
Unclassified (1)	+	+	-	-	-	+
Unclassified (4)	+	+	-	-	-	-

HBV Classification (n)	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc Total	Anti-HBe	Anti-HBs (> 10 mIU/mL)
Unclassified (1)	-	-	Equivocal	-	-	-
Unclassified (1)	-	-	Equivocal	+	+	-
Unclassified (2)	-	-	Equivocal	+	+	+
Unclassified (1)	+	-	Equivocal	+	+	-
Unclassified (1)	Conf Invalid	-	-	-	-	-
Unclassified (1)	-	+	-	+	+	+

+ = reactive

- = non-reactive

Samples from patients who fell into the following categories: acute, chronic, early recovery, recovery, immune natural infection (recovery), recovered, HBV vaccine response, not previously infected, and unknown serostatus categories, were included in the study and used for data analysis.

Thirty-five samples returned a result of unknown serological status (2.17%). The performance of the device was evaluated with the samples included.

Expected Values

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

• 619 patients (38.4%) were from the population considered at risk for hepatitis B (high risk) due to lifestyle, behavior, occupation, or known exposure events.

• 629 patients (39.0%) were from the signs and symptoms population

The ADVIA Centaur XP Anti-HBcT2 results for the prospective population for all sites combined by age group and gender are summarized below (Table 17).

Table 17: Expected Values with ADVIA Centaur XP

Age Range (Years)	Gender	Reactive		Nonreactive		Total Number Tested
		N[a]	%[b]	N	%	
21-30	Male	3	4.2	69	95.8	72
	Female	4	2.0	193	98.0	197
	Overall	7	2.6	262	97.4	269
31-40	Male	13	15.5	71	84.5	84
	Female	31	16.1	161	83.9	192
	Overall	44	15.9	232	84.1	276
	Male	48	34.3	92	65.7	140

41-50	Female	35	24.8	106	75.2	141
	Overall	83	29.5	198	70.5	281
51-60	Male	115	40.9	166	59.1	281
	Female	78	40.0	117	60.0	195
	Overall	193	40.5	283	59.5	476
61-70	Male	72	47.4	80	52.6	152
	Female	38	39.2	59	60.8	97
	Overall	110	44.2	139	55.8	249
71-92	Male	11	37.9	18	62.1	29
	Female	5	33.3	10	66.7	15
	Overall	16	36.4	28	63.6	44
Total	Male	262	34.6	496	65.4	758
	Female	191	22.8	646	77.2	837
	Overall	453	28.4	1142	71.6	1595

C. Safety and Effectiveness Results

Safety Results

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

Effectiveness Results

Prospective Population

The performance of the ADVIA CentaurAtellica Anti-HBcT2 assay was evaluated against the risk groups, the disease classification, and the subpopulations. The performance on the ADVIA Centaur XP, ADVIA Centaur CP, and Atellica IM instruments is presented separately and combined.

By Risk Group

The performance of the ADVIA Centaur/Atellica Anti-HBcT2 assay was evaluated in the signs and symptoms prospective populations on each assay system and compared to the reference assay (Tables 18 - 20). The percent agreement and confidence intervals for the prospective population by risk group is presented below (Tables 21 - 23).

1) Signs and Symptom prospective population:

Table 18: ADVIA Centaur XP -Comparison of Results in the Signs and Symptoms Prospective Population

ADVIA Centaur XP HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	189	12	201
Nonreactive	5	570	575

Total	194	582	776

% Positive Agreement = 97.4% (189/194)
95% Confidence Interval = 94.1%–98.9%
% Negative Agreement = 97.9% (571/583)
95% Confidence Interval = 96.4%–98.8%

Table 19: ADVIA Centaur XPT -Comparison of Results in the Signs and Symptoms Prospective Population

ADVIA Centaur XPT HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	189	14	203
Nonreactive	5	568	573
Total	194	582	776

% Positive Agreement = 97.4% (189/194)
95% Confidence Interval = 94.1%–98.9%
% Negative Agreement = 97.6% (568/582)
95% Confidence Interval = 96.0%–98.6%

Table 20: Atellica IM – Comparison of Results in the Signs and Symptoms Prospective Population

Atellica IM 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 21: ADVIA Centaur XP -Comparison of Results in the High-Risk Prospective Population

ADVIA Centaur XP HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	245	7	252
Nonreactive	4	563	567
Total	249	570	819

% Positive Agreement = 98.4% (245/249)
95% Confidence Interval = 95.9%–99.4%
% Negative Agreement = 98.8% (563/570)
95% Confidence Interval = 97.5%–99.4%

Table 22: ADVIA Centaur XPT – Comparison of Results in the High-Risk Prospective Population

ADVIA Centaur XPT HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	246	8	254
Nonreactive	3	562	565
Total	249	570	819

% Positive Agreement = 98.8% (246/249)
95% Confidence Interval = 96.5%–99.6%
% Negative Agreement = 98.6% (562/570)
95% Confidence Interval = 97.3%–99.3%

Table 23: Atellica IM – Comparison of Results in the High-Risk Prospective Population

Atellica IM HBcT2 Assay	Reference Assay		Total
	Reactive	Nonreactive	
Reactive	244	5	249
Nonreactive	5	565	570
Total	249	570	819

% Positive Agreement = 98.0% (244/249)
95% Confidence Interval = 95.4%–99.1%
% Negative Agreement = 99.1% (565/570)
95% Confidence Interval = 98.0%–99.6%

a. By HBV Serological Classification

A total of 1595 samples including the 35 unclassified serostatus samples were evaluated using the ADVIA Centaur/Atellica Anti-HBcT2 assay on the ADVIA Centaur XP, XPT, and Atellica IM and a reference aHBcT assay for each sample classification (Table 16). The agreement and 95% CIs between the ADVIA Centaur/Atellica IM Anti-HBcT2 assay and a reference aHBcT assay for each HBV classification are presented in the Tables 24 - 26.

Table 24: Positive and Negative Percent Agreements Between ADVIA Centaur XP HBcT2 assay and reference aHBcT assay by HBV Classification

ADVIA Centaur XP 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%	(6/14)	42.9%	21.4-67.4%
Recovery, N=105	(101/101)	100%	96.3-100%	(3/4)	75.0%	30.1-95.4%
HBV Vaccine Response, N=539	(20/25)	80.0%	60.9-91.1%	(509/514)	99.0%	97.7-99.6%
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%	(24/26)	92.3%	75.9-97.9%

Total, N=1595	(434/443)	98.0%	96.2-98.9%	(1133/1152)	98.4%	97.4-98.9%

Table 25: Positive and Negative Percent Agreements Between ADVIA Centaur XPT HBcT2 assay and reference aHBcT assay by HBV Classification

ADVIA Centaur XPT 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%	43.9-100.0%	NA	NA	NA
Chronic, N=77	(77/77)	100%	95.2-100.0%	NA	NA	NA
Early Recovery, N=15	(15/15)	100%	79.6-100.0%	NA	NA	NA
Recovered, N=223	(207/209)	99.0%	96.6-99.7%	(6/14)	42.9%	21.4-67.4%
Recovery, N=105	(101/101)	100%	96.3-100.0%	(3/4)	75.0%	30.1-95.4%
HBV Vaccine Response, N=539	(20/25)	80.0%	60.9-91.1%	(509/514)	99.0%	97.7-99.6%
Not Previously Infected, N=599	(3/5)	60.0%	23.1-88.2%	(589/594)	99.2%	98.0-99.6%
Unclassified, N=34	(8/8)	100%	67.6-100.0%	(23/26)	88.5%	71.0-96.0%
Total, N=1595	(434/443)	98.0%	96.2-98.9%	(1133/1152)	98.4%	97.4-98.9%

Table 26: Positive and Negative Percent Agreements Between Atellica IM HBcT2 assay and reference aHBcT assay by HBV Classification

Atellica IM Analyzer 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%	43.9-100.0%	NA	NA	NA
Chronic, N=77	(77/77)	100%	95.2-100.0%	NA	NA	NA
Early Recovery, N=15	(15/15)	100%	79.6-100.0%	NA	NA	NA
Recovered, N=223	(207/209)	99.0%	96.6-99.7%	(7/14)	50.0%	26.8-73.2%
Recovery, N=105	(101/101)	100%	96.3-100.0%	(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%	(24/26)	92.3%	75.9-97.9%
Total, N=1595	(433/443)	97.7%	95.9-98.8%	(1136/1152)	98.6%	97.8-99.1%

b. Pregnant Population

Serum samples from United States were included in the study (N = 193). Samples were tested from pregnant women with either signs and symptoms of hepatitis B or with risk factors for HBV infection, who were in the first (62/193, 32.1%), second (61/193, 31.6.0%), or third trimester (70/193, 36.3%) of pregnancy. Results of the testing (reactive and nonreactive) were compared using the ADVIA Centaur HBcT2 assay and the reference HBcT assay for the prenatal population in their first, second, and third trimester, for all testing sites:

Table 27: Percent Agreement and Confidence Intervals: Prenatal Populations

Trimester	**Positive Agreement**		**Negative Agreement**	
	% (x/n)	**95% CI**	**% (x/n)**	**95% CI**
First	100% (2/2)	34.2%-100%	100% (60/60)	94.0%-100%
Second	100% (6/6)	61.0%-100%	98.2% (54/55)	90.4%-99.7%
Third	100% (2/2)	34.2%-100%	100% (68/68)	94.7%-100%
Total	100% (10/10)	72.2%-100%	99.5% (182/183)	97.0%-99.9%

Pediatric Extrapolation

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

D. 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 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.

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 adults.

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 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 July 27, 2022.

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.