SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Antibody to Hepatitis B e Antigen Assay (Anti-HBe)
Device Trade Name:	ADVIA Centaur® Anti-HBe2 (aHBe2) assay
Device Product Code:	LOM
Applicants Name and Address:	Siemens Healthcare Diagnostics Inc. 511 Benedict Ave Tarrytown, NY 10591
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P200017
Date of FDA Notice of Approval:	July 14, 2021

II. INDICATIONS FOR USE

The ADVIA Centaur® Anti-HBe2 (aHBe2) assay is an in vitro diagnostic immunoassay for the qualitative detection of antibodies to the e antigen of the hepatitis B virus (HBV) in human pediatric (2–21 years old) and adult serum, EDTA plasma, or lithium heparin plasma using the ADVIA Centaur systems (XP/XPT/CP). Assay results, in conjunction with other laboratory results and clinical information may be used as an aid in the diagnosis of hepatitis B virus (HBV) infection in patients with signs or symptoms of hepatitis B infection, or with risk factors for HBV infection, or with known HBV infection. Results of the assay, in conjunction with other diagnostic information, may be used to aid in determining HBV seroconversion.

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).

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warning and precautions can be found in the ADVIA Centaur® Anti-HBe2 (aHBe2) assay package insert.

- For *in vitro* diagnostic use.
- For Professional Use.
- For Prescription Use Only.
- Warning - May cause an allergic skin reaction. Wear protective gloves/protective clothing/eye protection/face protection. IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs: Get medical advice/attention. Take off contaminated clothing and wash it before reuse.
- Caution Potential Biohazard - Contains human source material. Each donation of human blood or blood component negative for antibodies to HBe antigen was tested by FDA-approved methods for the presence of antibodies to human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), as well as for hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (HCV). The test results were negative (not repeatedly reactive). No test offers complete assurance that these or other infectious agents are absent; this material should be handled using good laboratory practices and universal precautions.

  Calibrators and controls contain processed human plasma that is nonreactive for HIV and HCV but is reactive for antibodies to HBe antigen. The units were treated with a BPL-UV inactivation procedure;10 however, all products manufactured using human source material should be handled as potentially infectious.
- Caution - This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

V. DEVICE DESCRIPTION

Assay Principle and Format:

The ADVIA Centaur aHBe2 assay is a fully automated 2-step competitive immunoassay using chemiluminescent technology

The Ancillary well reagent contains recombinant HBeAg. The Solid Phase contains microparticles coated with aHBe monoclonal antibody. The Lite Reagent contains aHBe monoclonal antibody labeled with acridinium ester.

The sample is incubated with the Ancillary Well Reagent. During the incubation period, aHBe in the sample binds with recombinant HBeAg. The Solid Phase and Lite Reagent are added next and

bind any recombinant HBeAg not already bound by sample. After a wash step, acid and base are dispensed to initiate the chemiluminescent reaction.

An inverse relationship exists between the amount of aHBe activity 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 a cut-off of 1.00 Index established with the calibrators.

The ADVIA Centaur XP system automatically performs the following actions:

1. Dispenses 75 µL of sample into a cuvette.
2. Dispenses 75 µL of Ancillary Well Reagent and incubates the mixture for 29 minutes at 37°C.
3. Dispenses 150 µL of Solid Phase and 75 µL of Lite Reagent, and incubates the mixture for 18 minutes at 37°C.
4. Separates, aspirates, then washes the cuvette with ADVIA Centaur Wash
5. Dispenses 300 µL each of ADVIA Centaur Acid Reagent and ADVIA Centaur Base Reagent to initiate the chemiluminescent reaction.
6. Reports results.

Calibration:

The ADVIA Centaur aHBe2 assay utilizes two-point calibration using the two calibrators (Calibrator L, Calibrator H) provided with each kit. There are two levels, the low calibrator (Calibrator L (~ 0.5 Index)) and the high calibrator (Calibrator H (~ 1.5 Index)). When used with the ADVIA Centaur aHBe2 reagent, there is an emission of light which can be measured by the ADVIA Centaur luminometer.

The ADVIA Centaur aHBe2 calibrators are value assigned over multiple runs on the ADVIA Centaur instruments using a specific lot of reagent and against internal standards. Results are reported in Index value. 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.

Calibration frequency- The two calibrators in the kit are run when one or more of the following conditions exist:

- At the end of the 21-day calibration interval.
- When changing lot numbers of primary reagent packs.
- When indicated by quality control results.
- After major maintenance or service, as indicated by quality control results.

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 aHBe while those below 1.00 are non-reactive.

Controls:

ADVIA Centaur Anti-HBe2 QC set contains Negative control (2 vials with 10 mL) and Positive control (2 vials with 10 mL). They have different concentrations of anti-HBe antibodies and the Index (Negative control (~0.3 Index) and Positive control (~2.00 Index)) for each control is indicated in a Control Expected Value card enclosed with the kit. The performance of the ADVIA Centaur aHBe2 assay is monitored by the use of Centaur aHBe2 Quality Controls at least once during each day when samples are analyzed or after a successful calibration.

Interpretation of Results:

The sample results from the ADVIA Centaur aHBe2 assay are in Index Values and they are reported by the system as 'Non-reactive' or 'Reactive.' The final interpretation of the results is done as shown below in Table 1.

Table 1. Interpretation of Results for the ADIVIA Centaur aHBe2 Assay

Initial Test Results (C/S)	Retest Zone	Final Interpretation
< 0.80	Not Required	Non-Reactive (Negative)
≥ 0.80 and < 1.20	Retest in duplicate	Sample is non-reactive and presumed negative for anti-HBe if 2 of 3 results are <1.00. Sample is reactive and presumed positive for anti-HBe if 2 of 3 results are ≥ 1.00.
≥ 1.20	Not Required	Reactive (Positive)

Components of the ADVIA Centaur® Anti-HBe2 (aHBe2) Assay

1. **Reagent Kit:**

Each ADVIA Centaur Anti-HBe2 kit contains a ReadyPack for 50 tests and one vial each of two calibrators (Calibrator L and Calibrator H). The calibrators provided in the kit are matched to the ReadyPack primary reagent. The kit also provides ADVIA Centaur aHBe2 Master Curve card and aHBe2 CAL calibrator assigned value card and barcode labels.

ADVIA Centaur Anti-HBe2 ReadyPack – Number of Tests – 50

- **Lite reagent: 3.8 mL/reagent pack.**

  Mouse monoclonal anti-HBe labeled with an acridinium ester in buffer, bovine serum albumin (BSA); mouse IgG; surfactant; preservative Proclin 950 1.5 mL/L.
- **Solid phase: 7.5 mL/reagent pack**

  Paramagnetic microparticle suspension coated with mouse monoclonal aHBe in buffer; BSA, surfactant; sodium azide (< 0.1%).
- **Ancillary reagent: 3.8 mL/reagent pack**

Recombinant HBe antigen in buffer; BSA; surfactant; preservative Proclin 950 1.5 mL/L.

ADVIA Centaur Anti-HBe2 Calibrator

Processed human plasma negative and positive for aHBe; sodium azide (< 0.1%)

- **aHBe2 CAL low calibrator: 2.0 mL/vial**
- **aHBe2 CAL high calibrator: 2.0 mL/vial**

Additional materials required but purchased separately

2. **ADVIA Centaur aHBe2 Quality Control Kit:**

Negative Control: 2 x 10.0 mL, Level 1
Positive Control: 2 x 10.0 mL, Level 2
Quality control lot-specific value sheet and barcode labels.

3. **ADVIA Centaur Probe Wash 3:**

50.0 mL/pack
Sodium hypochlorite (0.5%); sodium hydroxide (<0.5%), pH 11.0

4. **ADVIA Centaur Wash 1:**

1500 mL/pack
Phosphate buffered saline; sodium azide (< 0.1%); surfactant

5. **ADVIA Centaur Wash 1:**

2500 mL/Pack
Phosphate buffered saline; sodium azide (< 0.1%); surfactant

6. **Instrumentation and Software:**

The ADVIA Centaur CP and ADVIA Centaur XP systems were cleared under k041133 and k032525. The ADVIA Centaur XPT is an upgraded model and instrument family member of the XP system cleared under k141999.

The Siemens ADVIA Centaur XP, ADVIA Centaur XPT and ADVIA Centaur CP System are automated immunoassay analyzers designed to perform in vitro diagnostic immunochemical assay analysis on clinical specimens and intended for professional use in a laboratory environment only. The system menu includes endocrine, anemia, allergy, reproductive, cardiovascular, oncology, adrenal, bone metabolism, therapeutic drug, and infectious disease assays. All assays are based on chemiluminescent technology. The ADVIA Centaur CP, ADVIA Centaur XP and ADVIA Centaur XPT Systems perform the following functions:

- Aspirates and dispenses samples
- Performs dilutions
- Adds reagents
- Incubates reaction vessels
- Separates solid and liquid wastes
- Measures photon emissions

- Performs data reduction
- Collects and maintains patient demographics and results.

The ADVIA Centaur XP, XPT and CP systems are automated and perform different functions including loading samples, primary and ancillary reagents, and supplies, or emptying waste without pausing or interrupting test processing.

The ADVIA Centaur XP, XPT and CP computers control system functions and processes data. The applications module is equipped with a CD-RW drive for software updates and for data storage. The ADVIA Centaur System software are the set of computer instructions that interprets system and assay information, calculates results, and provides the interface for controlling the system hardware.

The ADVIA Centaur XP software provides user interface workstation to control the operation of the system. The workspace has a system view offering access to system functions and an applications view offering access to a set of applications including the ADVIA QC analyzer, the RealTime Solutions service (e.g., remote troubleshooting and repair) and the online documentation browser.

Off-The-Shelf software components are integrated into the overall design of the ADVIA Centaur CP, ADVIA Centaur XP and ADVIA Centaur XPT software and as a result do not function outside of the software. The end user has no direct interaction with the OTS software components but instead with the overall design of the ADVIA Centaur CP, ADVIA Centaur XP and ADVIA Centaur XPT software.

Additional details can be found in the ADVIA Centaur XP, XPT or CP Operating Instructions Manual.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the determination of HBV infection and its disease stage. Detection of anti-HBe 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 in conjunction with clinical assessment and other laboratory test results in the diagnosis of the HBV infection. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The ADVIA Centaur aHBe2 assay has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The potential adverse effects associated with the use of this device are as follows. Failure of the product to perform as indicated or human error in use of the product may lead to a false result. Anti-HBe antibody is an intermediate or long-term risk analyte; repeatedly erroneous false positive or false negative anti-HBe results could lead to inappropriate initiation or cessation of antiviral therapy. 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. No specific adverse effects occurred during the conduct of clinical studies.

IX. SUMMARY OF NON-CLINICAL STUDIES

The software versions used for the studies described below were ADVIA Centaur CP (v6.4), ADVIA Centaur XP (v7.4.0.4) and ADVIA Centaur XPT (v1.5.1).

Cut-Off Determination

A set of 2111 samples that had been previously tested and classified as Positive (204) or Negative (1907) using the FDA-approved Reference Assay (Anti-HBe Assay) were tested with the ADVIA Centaur Anti-HBe2 assay on ADVIA Centaur XP system to determine the Cut-Off.

For each sample, sensitivity (TP rate) and specificity (TN rate) versus the Reference Assay was calculated, using the individual RLU of ADVIA Centaur Anti-HBe2 result as a tentative Cut-Off.

The optimal ADVIA Centaur aHBe2 Cut-Off was obtained considering the best results of the area under the ROC (Receiver Operating Characteristic) curve in terms of discrimination between positive and negative samples according to the reference method and considering the criterion of maximize the relative sensitivity and specificity.

The ADVIA Centaur aHBe2 assay Cut-Off (1.00 Index) was established at 214986 RLU, because it showed a good Sensitivity without compromising the Specificity. The percent positive agreement and percent negative agreement with the reference assay used to determine the cut-off were ≥ 95.0%.

Precision

The precision study for the ADVIA Centaur Anti-HBe2 assay was conducted in various sample matrices in a 20-day precision protocol using three lots of the reagents on ADVIA Centaur XP, XPT and CP instruments. Two controls (Positive & Negative) and four specimens in three matrices (serum, EDTA plasma, and lithium heparin plasma) were used to measure the precision of the assay at different dose levels. The specimens were assayed in duplicate per run, two runs per day for 20 days (N = 80 for each sample).

Four samples for each matrix was selected at different nominal values: sample 1, 0.50-0.79 (high non-reactive), sample 2, 0.80-1.20 (Cut-Off), sample 3, 1.21-1.70 (Reactive) and sample 4, > 1.70 (High Reactive).

The results in the following tables are with one lot of the ADVIA Centaur Anti-HBe2 assay on XP instrument. Calculations for within-run, between-run, between-day, and total precision were performed according to CLSI Document EP05-A3.

The repeatability of the combined three lots of ADVIA Centaur Anti-HBe2 assay ranged from 0.8% to 4.9%. The within-laboratory %CV of the combined three lots ranged from 1.3% to 9.6%. The results obtained with three lots of Reagent on ADVIA Centaur XP (Table 2A), XPT (Table 2B) and CP (Table 2C) instruments for repeatability and within-laboratory, indicating only minor variability in the components evaluated.

Table 2A. Centaur XP - Summary of Precision Results for the ADVIA Centaur Anti-HBe2 Assay

Sample Description	Mean (Index)	Within-Run		Between-Run		Between-Day		Total	
		SD[a]	CV[b] %	SD	CV %	SD	CV %	SD	CV %
EDTA plasma 1	0.71	0.01	1.7%	0.01	0.8%	0.01	1.8%	0.02	2.6%
EDTA plasma 2	1.06	0.01	1.2%	0.01	1.1%	0.01	1.2%	0.02	2.0%
EDTA plasma 3	1.41	0.02	1.7%	0.02	1.2%	0.01	0.5%	0.03	2.2%
EDTA plasma 4	1.91	0.02	1.0%	0.03	1.3%	0.00	0.0%	0.03	1.6%
Lithium Heparin plasma 1	0.61	0.01	2.1%	0.01	2.3%	0.01	1.5%	0.02	3.4%
Lithium Heparin plasma 2	1.02	0.02	1.5%	0.02	1.6%	0.01	0.6%	0.02	2.3%
Lithium Heparin plasma 3	1.43	0.02	1.3%	0.01	0.9%	0.01	0.9%	0.03	1.8%
Lithium Heparin plasma 4	1.96	0.03	1.5%	0.02	1.2%	0.00	0.0%	0.04	1.9%
Serum 1	0.54	0.01	1.9%	0.01	1.5%	0.01	1.8%	0.02	3.0%
Serum 2	0.84	0.01	1.6%	0.03	3.5%	0.00	0.0%	0.03	3.9%
Serum 3	1.44	0.02	1.4%	0.02	1.3%	0.01	0.6%	0.03	2.0%
Serum 4	2.00	0.04	1.7%	0.02	1.0%	0.02	0.9%	0.04	2.2%
Negative Control	0.28	0.01	3.1%	0.01	3.5%	0.01	3.8%	0.02	6.0%
Positive Control	1.96	0.02	1.2%	0.01	0.6%	0.01	0.7%	0.03	1.5%

[a] Standard deviation of mean concentration (Index)
[b] Coefficient of variation

Table 2B. Centaur XPT - Summary of Precision Results for the ADVIA Centaur Anti-HBe2 Assay

Sample Description	Mean (Index)	Within-Run		Between-Run		Between-Day		Total	
		SD[a]	CV[b] %	SD	CV %	SD	CV %	SD	CV %
EDTA plasma 1	0.74	0.02	2.9%	0.01	1.3%	0.03	4.3%	0.04	5.3%
EDTA plasma 2	1.07	0.03	3.1%	0.03	3.2%	0.03	2.8%	0.06	5.3%
EDTA plasma 3	1.45	0.03	2.1%	0.03	1.7%	0.03	2.1%	0.05	3.4%
EDTA plasma 4	1.99	0.06	2.9%	0.03	1.6%	0.03	1.7%	0.07	3.7%
Lithium Heparin plasma 1	0.63	0.02	3.2%	0.02	3.6%	0.02	2.5%	0.03	5.4%
Lithium Heparin plasma 2	1.06	0.02	2.1%	0.03	2.4%	0.03	3.0%	0.05	4.4%
Lithium Heparin plasma 3	1.47	0.03	2.0%	0.03	1.9%	0.04	2.6%	0.06	3.8%
Lithium Heparin plasma 4	2.04	0.07	3.4%	0.01	0.6%	0.04	1.9%	0.08	4.0%
Serum 1	0.55	0.02	2.8%	0.02	4.2%	0.02	4.4%	0.04	6.8%
Serum 2	0.84	0.03	3.0%	0.03	3.3%	0.02	2.3%	0.04	5.0%
Serum 3	1.47	0.03	1.8%	0.04	2.7%	0.02	1.3%	0.05	3.5%
Serum 4	2.08	0.07	3.2%	0.02	1.1%	0.04	2.0%	0.08	4.0%
Negative Control	0.28	0.01	4.7%	0.01	5.1%	0.02	6.6%	0.03	9.6%
Positive Control	2.04	0.05	2.4%	0.03	1.6%	0.04	2.0%	0.07	3.5%

[a] Standard deviation of mean concentration (Index)
[b] Coefficient of variation

Table 2C. ADVIA Centaur CP - Summary of Precision Results for the ADVIA Centaur Anti-HBe2 Assay

Sample Description	Mean (Index)	Within-Run		Between-Run		Between-Day		Total	
		SD[a]	CV[b] %	SD	CV %	SD	CV %	SD	CV %
EDTA plasma 1	0.72	0.01	1.2%	0.01	1.9%	0.01	0.9%	0.02	2.4%
EDTA plasma 2	1.06	0.02	2.1%	0.01	1.2%	0.01	0.7%	0.03	2.5%
EDTA plasma 3	1.44	0.02	1.2%	0.02	1.4%	0.01	0.9%	0.03	2.1%
EDTA plasma 4	1.97	0.02	1.1%	0.03	1.3%	0.04	1.9%	0.05	2.5%
Lithium Heparin plasma 1	0.62	0.01	1.3%	0.01	1.7%	0.01	2.1%	0.02	3.0%

Lithium Heparin plasma 2	1.03	0.01	1.1%	0.02	1.4%	0.01	0.8%	0.02	1.9%
Lithium Heparin plasma 3	1.45	0.01	0.9%	0.02	1.1%	0.02	1.2%	0.03	1.8%
Lithium Heparin plasma 4	2.02	0.03	1.3%	0.02	0.9%	0.04	1.9%	0.05	2.5%
Serum 1	0.53	0.01	2.0%	0.01	2.1%	0.00	0.6%	0.02	3.0%
Serum 2	0.83	0.01	1.4%	0.02	2.1%	0.01	0.8%	0.02	2.7%
Serum 3	1.45	0.01	0.9%	0.02	1.6%	0.02	1.4%	0.03	2.3%
Serum 4	2.03	0.03	1.3%	0.03	1.4%	0.05	2.2%	0.06	2.9%
Negative Control	0.27	0.01	3.3%	0.00	1.2%	0.01	3.7%	0.01	5.1%
Positive Control	2.00	0.02	1.1%	0.03	1.3%	0.04	1.9%	0.05	2.6%

[a] Standard deviation of mean concentration (Index)
[b] Coefficient of variation

System Reproducibility

The system reproducibility of the ADVIA Centaur Anti-HBe2 assay was evaluated on ADVIA Centaur XP, XPT and CP systems at three external US sites. Each site tested at least two of the three reagent lots. A four-member serum panel was assayed in replicates of four with two runs per day, over five days for each lot (N = 240) for each sample. The system reproducibility was determined in accordance with CLSI Document EP05-A3 *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition*. The % CV for reproducibility for the three sites are ranged between 2.3% –10.0%. The results for ADVIA Centaur XP, XPT, and CP are summarized below in the Tables 3A, 3B and3C.

Table 3A. ADVIA Centaur XP - Summary of Anti-HBe2 Reproducibility Results

		Within-Run Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
Sample	Mean (Index)	SD[a]	CV[b] (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Serum 1	0.61	0.01	2.4	0.01	1.6	0.00	0.5	0.05	7.8	0.00	0.0	0.05	8.3
Serum 2	0.95	0.02	1.9	0.02	1.7	0.01	1.2	0.06	6.1	0.00	0.0	0.06	6.7
Serum 3	1.46	0.02	1.6	0.02	1.3	0.01	0.6	0.01	0.8	0.00	0.0	0.03	2.3
Serum 4	2.08	0.03	1.5	0.01	0.6	0.02	0.9	0.05	2.6	0.00	0.0	0.07	3.2
Negative Control	0.28	0.01	3.7	0.01	2.3	0.00	1.5	0.02	6.8	0.00	0.0	0.02	8.2
Positive Control	1.99	0.03	1.6	0.02	0.8	0.01	0.5	0.03	1.3	0.00	0.0	0.05	2.3

[a] Standard deviation of mean concentration (Index)

[b] Coefficient of variation

Table 3B. ADVIA Centaur XPT - Summary of Anti-HBe2 Reproducibility Results

Sample	Mean (Index)	Within-Run Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
		SD[a]	CV[b] (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Serum 1	0.60	0.01	2.3	0.01	1.2	0.01	1.0	0.05	8.3	0.00	0.0	0.05	8.8
Serum 2	0.93	0.02	1.6	0.02	1.7	0.00	0.0	0.05	5.9	0.00	0.0	0.06	6.4
Serum 3	1.44	0.02	1.7	0.02	1.1	0.00	0.2	0.01	0.4	0.02	1.4	0.04	2.5
Serum 4	2.01	0.03	1.4	0.01	0.3	0.01	0.5	0.03	1.4	0.05	2.3	0.06	3.1
Negative Control	0.28	0.01	4.0	0.01	2.3	0.00	0.0	0.01	2.4	0.01	2.4	0.02	5.7
Positive Control	1.96	0.03	1.3	0.02	0.9	0.00	0.0	0.03	1.5	0.03	1.7	0.05	2.7

[a] Standard deviation of mean concentration (Index)
[b] Coefficient of variation

Table 3C. ADVIA Centaur CP - Summary of Anti-HBe2 Reproducibility Results

Sample	Mean (Index)	Within-Run Repeatability		Between-Run		Between-Day		Between-Lot		Between-Site		Reproducibility	
		SD[a]	CV[b] (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Serum 1	0.60	0.01	2.3	0.01	2.2	0.01	0.8	0.05	8.2	0.02	4.1	0.06	9.7
Serum 2	0.95	0.02	2.5	0.03	3.3	0.00	0.0	0.05	5.4	0.00	0.0	0.06	6.8
Serum 3	1.46	0.03	2.1	0.03	2.0	0.00	0.9	0.01	0.4	0.02	1.5	0.05	3.3
Serum 4	2.07	0.06	3.0	0.02	0.8	0.02	1.1	0.04	1.7	0.02	0.8	0.08	3.8
Negative Control	0.28	0.01	5.2	0.01	2.7	0.01	1.9	0.01	2.3	0.02	7.6	0.03	10.0
Positive Control	2.01	0.05	2.7	0.03	1.6	0.02	1.1	0.00	0.2	0.02	0.8	0.07	3.4

[a] Standard deviation of mean concentration (Index)
[b] Coefficient of variation

The instrument family members XP, XPT and CPT demonstrated equivalent reproducibility (Table 4). The instruments demonstrated only minor variability in the components evaluated.

Table 4. ADVIA Centaur XP, XPT and CP - Summary of ADVIA Centaur Anti-HBe2 Reproducibility Results

System	Sample	% CV Reproducibility
ADVIA CENTAUR XP	Serum 1	8.3%
	Serum 2	6.7%
	Serum 3	2.3%
	Serum 4	3.2%
	Negative Control	8.2%
	Positive Control	2.3%
ADVIA CENTAUR XPT	Serum 1	8.8%
	Serum 2	6.4%
	Serum 3	2.5%
	Serum 4	3.1%
	Negative Control	5.7%
	Positive Control	2.7%
ADVIA CENTAUR CP	Serum 1	9.7%
	Serum 2	6.8%
	Serum 3	3.3%
	Serum 4	3.8%
	Negative Control	10.0%
	Positive Control	3.4%

Sensitivity/Seroconversion Panels

The seroconversion sensitivity of the ADVIA Centaur Anti-HBe2 assay was evaluated by testing three commercially available HBV patient seroconversion panels in replicates on ADVIA Centaur XP, XPT, and CP instruments, and the FDA-approved reference assay. The performance of the

ADVIA Centaur Anti-HBe2 assay on all three instruments matched the performance of the reference assay (Table 5):

Table 5. Summary of ADVIA Centaur Anti-HBe2 Panel Results

Panel ID	aHBe Reactive Result from Initial Draw Date		ADVIA Centaur Assay vs. Reference Assay
	Reference Assay (Days)	ADVIA Centaur Assay (Days)	Difference in Bleed Days (Numbers)[a]
6510	70	70	0
SCP-HBV-001	88	88	0
SCP-HBV-002	74	74	0

[a] The difference in bleed numbers is relative to the reference assay. For example, a +2 means that the reference assay required 2 additional bleeds before reactivity was determined as compared to the time-point when ADVIA Centaur assay confirmed reactive.

Analytical Sensitivity/Dilution Study with Standard

The analytical sensitivity was assessed with two lots of ADVIA Centaur Anti-HBe2 kits by testing a series of dilutions of a Paul Ehrlich Institute (PEI) Standard (WHO 1st International Standard Anti-Hepatitis B virus e antigen) on ADVIA Centaur XP, XPT and CP systems. A stock solution of standard PEI 120 IU/mL was used to prepare dilution series using negative human serum at concentrations ranging from 1.00 to 0.00 PEI IU/mL. Linear regression was used to determine the concentration of the PEI reference sample that corresponds to the ADVIA Centaur Anti-HBe2 assay cut-off (Index = 1.00). Analytical sensitivity evaluated with two different reagent lots of ADVIA Centaur Anti-HBe2 on ADVIA Centaur XP, CP and XPT instruments only minor differences from the WHO International Standard in all cases, as shown below in Table 6.

Table 6. ADVIA Centaur XP, XPT and CP - Concentration at the Cut-Off

Reagent Lot	IU/mL at Cut-Off		
	Platform		
	ADVIA Centaur	ADVIA Centaur XPT	ADVIA Centaur CP
B30919	0.17	0.17	0.16
B30775	0.17	0.18	0.16

Endogenous Interference

Testing was performed in accordance with CLSI Documents EP07-A3*, Interference Testing in Clinical Chemistry, Third Edition,* and EP37, *Supplemental Tables for Interference Testing*.

The sensitivity of the ADVIA Centaur Anti-HBe2 assay to interference by endogenous substances was evaluated at the concentrations indicated in Table 7. The study was performed using one lot of reagents to test each interferant on an ADVIA Centaur XP system with serum, EDTA plasma and Lithium Heparin plasma matrices. The reactivity of a pool of samples was spiked with the substance being tested (Test) and compared to the reactivity of the same pool of samples spiked with the solvent or media (Control) used for the substance. The bias was calculated as percentage of (Test-Control)/Control. The results of the interference study concluded that the following substances at the tested concentrations do not interfere with the ADVIA Centaur Anti-HBe2 assay using the three tested sample matrices (serum, EDTA plasma and Lithium Heparin plasma).

Table 7. Summary of Endogenous Substances used in the Interference Study

Substance	Substance Test Concentration Units
Bilirubin conjugated (icteric)	40 mg/dL
Bilirubin unconjugated (icteric)	40 mg/dL
Biotin	3500 ng/mL
Cholesterol	400 mg/dL
Hemoglobin (hemolyzed)	1000 mg/dL
Lipemia (glyceryl trioleate)	3000 mg/dL
Lipemia (intralipid)	3000 mg/dL
Protein (hyperproteinemic)	12 g/dL
Protein (hypoproteinemic)	3 g/dL

Analytical Specificity (Cross-Reactivity)

The ADVIA Centaur Anti-HBe2 assay was evaluated on ADVIA Centaur XP system for potential cross-reactivity with viral antibodies or other cross-reactants in the specimens from individuals with medical conditions unrelated to the HBV infection. A total of 314 samples from 33 unrelated medical conditions were tested in singlicate with one reagent lot of the ADVIA Centaur Anti-HBe2 assay and an FDA-approved Anti-HBe Assay (Reference Assay) to determine the true status of the samples.

Three samples were identified as equivocal by ADVIA Centaur Anti-HBe2 in the first analysis and they were re-tested in duplicate. The repeated results from these three samples were concordant with reference Anti-HBe results. One HCV sample was identified as discrepant in the first analysis. The sample was analyzed in duplicate by ADVIA Centaur Anti-HBe2 and the reference assay and was confirmed as a discrepant sample. Finally, it was tested in singlicate by a

second FDA-approved assay. The sample was resolved as concordant with ADVIA Centaur Anti-HBe2 assay.

The Cross Reactivity by other disease conditions study demonstrates agreement between the ADVIA Centaur Anti-HBe2 assay and the Reference Assays (Table 8) except for the single HCV sample that was concordant with the second reference assay. Hence, no interference was observed with the concentrations tested.

Table 8. Summary of Cross-Reactivity Testing

Clinical Category	Number Tested	Reactive	
		ADVIA Centaur Assay	FDA-approved aHBe Assay
Alanine amino transferase (ALT)	10	0	0
Anti-nuclear antibodies (ANA)	10	0	0
Cytomegalovirus (CMV) IgG	6	0	0
Cytomegalovirus (CMV) IgM	14	0	0
Dialysis patients	10	0	0
Escherichia coli	10	0	0
Epstein Barr Virus (EBV) VCA IgG	10	0	0
Epstein Barr Virus (EBV) VCA IgM	10	0	0
Flu vaccinated	10	0	0
HAV IgG Total	10	1	1
HBsAg vaccinated	10	1	1
Hepatitis C Virus (HCV)	10	1	1*
Herpes Simplex Virus (HSV-1)	10	0	0
Herpes Simplex Virus (HSV-2)	10	0	0
Heterophile antibodies	10	0	0
Human Herpes Virus 6 (HHV-6)	9	0	0
Human Herpes Virus 8 (HHV-8)	10	0	0
Human Immunodeficiency Virus -1	10	0	0
Human Immunodeficiency Virus -2	10	3	3
Human Anti-Mouse Antibodies (HAMA)	10	0	0
Multi-parous females	10	1	1
Multiple Myeloma	10	0	0
Non-viral liver disease	10	0	0
Pregnant females	10	0	0
Rheumatoid Arthritis	10	0	0
Rheumatoid Factor (RF)	10	1	1
Rubella IgG	10	0	0

Syphilis (total or IgG)	10	1	1
Toxoplasma gondii IgG	10	0	0
Toxoplasma gondii IgM	5	0	0
Urinary Tract Infection (UTI)	10	1	1
Varicella zoster virus (VZV) IgG	5	0	0
Varicella zoster virus (VZV) IgM	5	0	0

* concordant with the second reference assay

Sample Equivalence/Matrix Effect

The study was performed on the ADVIA Centaur XP instrument to assess the influence of different matrices on the results of the ADVIA Centaur Anti-HBe2 assay. Fifty matched sets of samples of different matrices (serum, serum separator tube (SST), EDTA plasma and Lithium Heparin plasma) from commercial sources were analyzed in duplicate in randomized order. The titers of the 25 reactive (>1 Index) and 25 non-reactive (<1 Index) samples were distributed throughout the range of the assay with 30 spanning the cutoff (0.70-1.60 Index). Because of the difficulty in obtaining samples throughout the ADVIA Centaur Anti-HBe2 assay measuring range (0.00-3.50 Index), 46 sets were prepared by spiking negative samples with different quantities of positive samples. The quantity of spiking material was always < 10% of the sample volume.

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 differences between matrices throughout the measurement range (Table 9).

Table 9. Summary of ADVIA Centaur Anti-HBe2 Sample Matrix Results

Tube	N	Sample Interval	Slope	Intercept (Index)	r
Dipotassium EDTA (plasma)	50	0.09–2.04 Index	0.93	-0.01	0.99
Lithium heparin (plasma)	50	0.08–2.08 Index	0.91	-0.01	0.99
Gel-barrier tube (serum)	50	0.13–2.24 Index	1.02	0.01	0.99

Reagent Carry-Over Study

To evaluate the specific susceptibility of the Anti-HBe2 and HBc assay carry-over, a study was performed to identify potential interferences due to reagent carryover between assays that are run-

in random-access mode, and to define mitigations required to permit assays that share the same reagent/ancillary probe(s) to be run-in random-access mode.

The reagent packs of ADVIA Centaur Anti-HBe2 were spiked into the assay reagents for different assays that use the same probe and conversely, the components of different ADVIA Centaur XP/CP assays were spiked into the new ADVIA Centaur Anti-HBe2 reagent packs for testing. Controls (Positive and Negative) were used as the samples in the study.

Results indicated that the Anti-HBe2 assay affected the HBeAg, TSTO (Testosterone) and HBcT assays. Mitigation using a Wash Pack in addition to the default water wash were successfully validated for all interferences observed and were implemented into the ADVIA Centaur XP and ADVIA Centaur CP Test Definitions. After mitigation no carryover was detected.

Stability Studies

a. Sample Stability

Studies were performed to determine the stability of patient samples under different storage conditions. Three matrices (serum or serum separator tube (SST), EDTA plasma, and Lithium-Heparin plasma) were analyzed on an ADVIA Centaur XP instrument with one lot of ADVIA Centaur Anti-HBe2 assay reagents. The effect of multiple freeze/thaw cycles and time to centrifugation on the stability of the samples was also evaluated.

Ten samples per matrix per study were used to evaluate sample handling and storage temperature, and freeze/thaw cycles. Fifteen samples/matrix were used for time to centrifugation studies, with the following distribution:

- 3 Non-reactive samples (≤ 0.69 Index)
- 2 samples between 0.70–1.00 Index (Below Cut off)
- 3 samples between 1.00–1.60 Index (Low Reactive)
- 2 samples > 1.60 Index.

The results of the sample handling and storage temperature studies, freeze/thaw, and long-term deep frozen (-70°C & -20°C) studies supported the claims for stability for all samples and matrices (serum or SST, EDTA plasma and Lithium Heparin plasma) (Table 10).

Table 10. Summary of the Results for the Sample Stability Study Types

Stability Study Type		Expiry
	Room Temperature (Nominal 25°C)	72 hours

Handling and Storage Temperature Studies	Refrigerated (2–8°C) in secondary containers	8 days
	Frozen (Nominal -20°C)	12 months
	Deep Frozen (Nominal -70°C)	12 months
	On Board Sample Stability	4 hours
	Primary Tube ("On the Clot")	7
Freeze/Thaw Cycles	Freeze Thaw (-20°C)	3 cycles
	Freeze Thaw (-70°C)	3 cycles
Time to Centrifugation		24 hours

B. Ambient Temperature Sensitivity

The accuracy of the test was evaluated on ADVIA Centaur XP and CP platforms to determine the effect of the ambient temperature changes (laboratory temperature) on assay performance. Ambient Temperature Sensitivity (ATS) was assessed at three different temperature set points: 18°C, 24°C and 30°C. All results demonstrated equivalent performance at ambient temperatures between 18°C and 30°C.

C. Reagent Stability

Reagent Real Time Stability Study (Shelf-Life)

Real time stability testing was performed on three lots of ADVIA Centaur Anti-HBe2 (reagent ReadyPack and kitted Calibrators) on ADVIA Centaur XP instrument to ascertain its shelf-life. Each lot was stored at 2–8°C and was tested at pre-determined checkpoints from T = 0 to 13 months. This is an on-going study. The results support the current shelf-life claim of 12 months for ADVIA Centaur Anti-HBe2 assay at 2–8°C.

Stability of the Calibration Interval

The stability of the working calibration curve was evaluated on the ADVIA Centaur XP and CP instruments with two lots of ADVIA Centaur Anti-HBe2. On day 0, eight ReadyPacks of the ADVIA Centaur Anti-HBe2 were placed on-board the ADVIA Centaur instrument and pierced. These ReadyPacks were kept on the instrument throughout the duration of the study. Moreover, on day 0 and every other checkpoint up to 61 days, one fresh ReadyPack was also loaded on the instrument. On each checkpoint, the Calibrators, Controls and Sample levels were randomly tested in triplicate using the on-board and the fresh ReadyPacks. The stability of the calibration was evaluated up to day 61. The results support the calibration interval claim of 21 days on ADVIA Centaur XP and CP instruments.

Reagent On-Board Stability

Studies were performed with two lots of ADVIA Centaur Anti-HBe2 to establish the maximum time that an opened ReadyPack can be stored on-board the ADVIA Centaur XP and CP instruments. On day 0, eight ReadyPacks of ADVIA Centaur Anti-HBe2, considered as opened packs, were placed on-board the instrument and pierced. The ReadyPacks were kept on the instrument throughout the duration of the study. Moreover, on day 0 and every other check day up to 61 days, one fresh ReadyPack was also tested on the instrument. Analysis of the Calibrators, Controls and Sample levels were performed with both the on-board and fresh packs in triplicate on day 0 and every checkpoint up to 61 days. The results support the Reagent on-board stability claim of 60 days on ADVIA Centaur XP and CP instruments.

Calibrators Open Vial Stability

The study was performed with two lots of the ADVIA Centaur Anti-HBe2 on ADVIA Centaur XP instrument to establish the open vial stability at 2–8°C of Calibrators versus the unopened vials. One calibration with each Opened Vial Calibrators set (OV: opened and squeezed each check day and then kept at 2–8°C) and one calibration with the Unopened Vial Calibrators set (UV: also kept at 2–8°C) were performed. An immutable (kept at below -70°C) set of controls with each calibration was analyzed in triplicate on day 0 and every other check day up to 61 days. The results support the Open Vial stability claim of 60 days for ADVIA Centaur Anti-HBe2 Calibrators.

Calibrator On-Board Stability

The on-board stability of Calibrators was evaluated with two lots of the Calibrators on one ADVIA Centaur XP instrument. The results of the controls were within the acceptance range on the calibration obtained up to 9 hours. 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 8 hours for the ADVIA Centaur Anti-HBe2 Calibrators on the ADVIA Centaur XP and CP instruments.

Animal Studies

Not applicable.

Additional studies

Not applicable.

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 anti-HBe2. 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 anti-HBe2 assay. The study consists of a Qualitative Method Comparison: Agreement with a reference assay (FDA-approved Anti-HBe assay).

The testing of the ADVIA Centaur Anti-HBe2 assay on the ADVIA Centaur XP, XPT and CP instruments, and the HBV serological classification were conducted at three external US sites with three reagent lots. The subject enrollment/sample collection was performed at or coordinated by four US clinical sites.

B. Study Population Demographics and Baseline Parameters

A total of 1877 subjects were enrolled for this study and prospective serum samples were collected. These included 180 pediatric subjects, the samples of 63 of which were spiked with adult reactive anti-HBe serum to generate contrived samples. Therefore, the prospective study population consisted of 1814 samples from unique patients including pediatric subjects (2 – 21 years old) as well as pregnant women (228). The samples from the pediatric subjects (<11–20, Table 16) were tested on the XP instrument only; therefore, there were 1697 subjects tested with the CP instrument.

The study population was considered either at high-risk for hepatitis B (due to lifestyle, behavior, occupation, or known exposure events) or was considered to have signs and symptoms of infection. The patients were divided by sex (55.5% female, 44.5% male). The study population was 27.1% Caucasian, 68.5% Black, 2.0% Asian, and 2.4% from unknown or other race. The mean age was 44 years (3–92 years). Patients in the study population were from the following geographic regions: Florida (34%), California (23.9%), Maryland (22.1%), Tennessee (6.4%), Georgia (5.3%), Nevada (3.9%), Massachusetts (3.5%), and other locations (0.9%).

ADVIA Centaur Anti-HBe2 assay was tested on all three platforms, ADVIA Centaur XP, XPT and CP systems and the agreement calculated against an FDA-approved aHBe reference assay. An overview of the detailed results in the following tables of the ADVIA Centaur Anti-HBe2 Percent Positive Agreement (PPA) and Negative Percentage of Agreement (NPA) versus the reference assay on the different instrument systems is below (Table 11).

Percent Agreement:
Positive and negative percent agreement between the ADVIA Centaur Anti-HBe2 assay and the FDA approved comparator anti-HBe test were calculated for subjects by HBV disease classification. Positive percent agreement with the comparator anti-HBe test was determined by dividing the number of reactive ADVIA Centaur Anti-HBe2 results by the total number of subjects positive with the comparator anti-HBe test. Negative percent agreement with the comparator anti-HBe test was determined by dividing the number of negative ADVIA Centaur Anti-HBe2 results by the total number of subjects negative with the comparator anti-HBe test.

Table 11. ADVIA Centaur XP, XPT and CP - ADVIA Centaur Anti-HBe2 Clinical Performance Results including Unknown Serostatus Samples

System	Parameter	Study Result	95% CI
ADVIA Centaur XP	PPA	97.6% (163/176)	87.5%–96.2%
	NPA	99.0% (1621/1638)	98.4%–99.4%
ADVIA Centaur XPT	PPA	92.0% (162/176)	87.1%–95.2%
	NPA	99.1% (1507/1521)	98.5%–99.5%
ADVIA Centaur CP	PPA	93.2% (164/176)	88.5%–96.1%
	NPA	99.0% (1506/1521)	98.4%–99.4%

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 a single specimen and the reactive (+) / nonreactive (-) patterns of six HBV reference serological markers obtained from two tests (Table 15): 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 26 unique reference marker patterns observed using the FDA-approved assays (Table 12).

Table 12. HBV Classification by Reference Markers (All Testing Sites) including Unknown Serostatus Samples

HBV Classification	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc Total	Anti-HBs	FDA-Approved anti-HBe Assay
Acute	+[a]	+	+	+	–[b]	–
Chronic	+	+	–	+	+	–
Chronic	+	+	–	+	–	–
Chronic	+	–	–	+	–	+
Chronic	+	–	–	+	–	–
Early Recovery	–	–	Equivocal	+	+	+
Early Recovery	–	–	+	+	+	+

Early Recovery	–	–	+	+	–	+
Recovery	–	–	–	+	–	+
Immune Natural Infection	–	–	–	+	+	+
Recovered	–	–	–	+	+	–
Recovered	–	–	–	+	–	–
HBV Vaccine Response	–	–	–	–	+	–
Not previously infected	–	–	–	–	–	–
Unknown	+	+	–	–	–	–
Unknown	+	+	Equivocal	+	–	–
Unknown	–	+	–	–	+	–
Unknown	–	+	–	–	–	–
Unknown	–	+	–	+	+	–
Unknown	–	+	–	+	–	–
Unknown	+	–	–	–	+	–
Unknown	–	–	–	–	–	+
Unknown	–	–	Equivocal	+	–	–
Unknown	–	–	+	–	–	–
Unknown	–	–	–	–	+	+
Unknown	–	–	+	+	+	–

[a] + = Reactive.
[b] – = Nonreactive

Samples from patients who fell into all of the 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-eight samples returned a result of unknown serological status (2.09%; 38/1814). This is a possible outcome from patient samples evaluated for disease classification that may be encountered in the clinic, but it was not clear how these should be included in the analysis. The performance of the device was evaluated primarily with the samples included, with additional information on performance with the samples excluded in the footnotes below the tables.

Expected Values

All of the samples from the 1814 unique patients including pediatric and pregnant women subjects were tested with the ADVIA Centaur Anti-HBe2.

- 784 patients (43.2%) were from the population considered at risk for hepatitis B (high risk) due to lifestyle, behavior, occupation, or known exposure events.
- 1030 patients (56.8%) were from the signs and symptoms population

The ADVIA Centaur Anti-HBe2 results for the prospective population for all sites combined by age group and gender are summarized below including with and without the unknown serostatus samples (Table 13).

Table 13. ADVIA Centaur XP - Distribution of Study Population by Age Group and Gender (All Testing Sites) including Unknown Serostatus Samples

Age Range (Years)*	Gender	Reactive		Nonreactive		Total Number Tested	Number without Unknown Serostatus Samples
		N	%	N	%		
< 11	Male	0	0.0	11	100	11	11
	Female	0	0.0	10	100	10	10
	Overall	0	0.0	21	100	21	21
11–20	Male	0	0.0	33	100	33	33
	Female	1	1.7	58	98.3	59	58
	Overall	1	1.1	91	98.9	92	91
21–30	Male	0	0.0	97	100	97	96
	Female	3	1.1	265	98.9	268	261
	Overall	3	0.8	362	99.2	365	357
31–40	Male	4	4.2	91	95.8	95	93
	Female	8	4.1	188	95.9	196	191
	Overall	12	4.1	279	95.9	291	284
41–50	Male	17	11.6	129	88.4	146	143
	Female	21	13.2	138	86.8	159	155
	Overall	38	12.5	267	87.5	305	298
51–60	Male	50	17.9	229	82.1	279	274
	Female	37	17.8	171	82.2	208	206
	Overall	87	17.9	400	82.1	487	480

Age Range (Years)*	Gender	Reactive		Nonreactive		Total Number Tested	Number without Unknown Serostatus Samples
		N	%	N	%		
61–70	Male	20	15.9	106	84.1	126	123
	Female	14	15.6	76	84.4	90	88
	Overall	34	15.7	182	84.3	216	211
71–92	Male	3	14.3	18	85.7	21	21
	Female	2	12.5	14	87.5	16	13
	Overall	5	13.5	32	86.5	37	34
Total	**Male**	**94**	**11.6**	**714**	**88.4**	**808**	**794**
	Female	**86**	**8.5**	**920**	**91.5**	**1006**	**982**
	Overall	**180**	**9.9**	**1634**	**90.1**	**1814**	**1776**

*CP did not test samples from pediatric subjects

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.

Efficacy Results

Prospective Population

The performance of the ADVIA Centaur Anti-HBe2 assay was evaluated against the risk groups, the disease classification, and the subpopulations. The performance on the XP and CP instruments is presented separately. The results from all testing sites are combined because the performance was equivalent across sites.

a. By Risk Groups

The performance of the ADVIA Centaur Anti-HBe2 assay was evaluated in the sign and symptom (Tables 14A, 14B and 14C) and high-risk (Tables 15A, 15B and 15C) prospective populations on each assay system and compared to the reference assay. The percent agreement and confidence intervals for the prospective population by risk group is presented below (Table 16A, 16B and 16C).

1) Signs and Symptom prospective population:

Table 14A. ADVIA Centaur XP - Comparison of Results in the Signs and Symptoms Prospective Population including Unknown Serostatus Samples

Reference Assay	ADVIA Centaur Anti-HBe2 Assay		
	Reactive	**Nonreactive**	**Total**
Reactive	111	8	119
Nonreactive	11	900	911
Total	**122**	**908**	**1030**

Table 14B. ADVIA Centaur XPT - Comparison of Results in the Signs and Symptoms Prospective Population including Unknown Serostatus Samples

Reference Assay	ADVIA Centaur Anti-HBe2 Assay		
	Reactive	**Nonreactive**	**Total**
Reactive	111	8	119
Nonreactive	10	843	853
Total	**121**	**851**	**972**

Table 14C. ADVIA Centaur CP - Comparison of Results in the Signs and Symptoms Prospective Population including Unknown Serostatus Samples

Reference Assay	ADVIA Centaur Anti-HBe2 Assay		
	Reactive	**Nonreactive**	**Total**
Reactive	111	8	119
Nonreactive	9	844	853
Total	**120**	**852**	**972**

2) High-Risk Prospective Population:

Table 15A. ADVIA Centaur XP - Comparison of Results in the High-risk Prospective Population including Unknown Serostatus Samples

Reference Assay	ADVIA Centaur Anti-HBe2 Assay		
	Reactive	**Nonreactive**	**Total**
Reactive	52	5	57
Nonreactive	6	721	727
Total	**58**	**726**	**784**

Table 15B. ADVIA Centaur XPT - Comparison of Results in the High-risk Prospective Population including Unknown Serostatus Samples

Reference Assay	ADVIA Centaur Anti-HBe2 Assay		
	Reactive	**Nonreactive**	**Total**
Reactive	51	6	57
Nonreactive	4	664	668
Total	**55**	**670**	**725**

Table 15C. ADVIA Centaur CP - Comparison of Results in the High-risk Prospective Population including Unknown Serostatus Samples

Reference Assay	ADVIA Centaur Anti-HBe2 Assay		
	Reactive	**Nonreactive**	**Total**
Reactive	53	4	57
Nonreactive	6	662	668
Total	**59**	**666**	**725**

Table 16A. ADVIA Centaur XP - Percent Agreement and Confidence Intervals (all testing sites) for Risk Groups including Unknown Serostatus Samples

Groups	Positive Agreement		Negative Agreement	
	% (x/n)	**95% CI**	**% (x/n)**	**95% CI**

Signs and Symptoms	93.3% (111/119)	87.3%–96.6%	98.8% (900/911)	97.9%–99.3%
High Risk	91.2% (52/57)	81.1%–96.2%	99.2% (721/727)	98.2%–99.6%
Total	**92.6% (163/176)**	**87.8%–95.6%**	**99.0% (1621/1638)**	**98.4%–99.4%**

Table 16B. ADVIA Centaur XPT - Percent Agreement and Confidence Intervals (all testing sites) for Risk Groups including Unknown Serostatus Samples

Groups	Positive Agreement		Negative Agreement	
	% (x/n)	**95% CI**	**% (x/n)**	**95% CI**
Signs and Symptoms	93.3% (111/119)	87.3%–96.6%	98.8% (843/853)	97.9%–99.4%
High Risk	89.5% (51/57)	78.9%–95.1%	99.4% (664/668)	98.5%–99.8%
Total	**92.0% (162/176)**	**87.1%–95.2%**	**99.1% (1507/1521)**	**98.5%–99.5%**

Table 16C. ADVIA Centaur CP - Percent Agreement and Confidence Intervals (all testing sites) for Risk Groups including Unknown Serostatus Samples

Groups	Positive Agreement		Negative Agreement	
	% (x/n)	**95% CI**	**% (x/n)**	**95% CI**
Signs and Symptoms	93.3% (111/119)	87.3%–96.6%	98.9% (844/853)	98.0%–99.4%
High Risk	93.0% (53/57)	83.3%–97.2%	99.1% (662/668)	98.1%–99.6%
Total	**93.2% (164/176)**	**88.5%–96.1%**	**99.0% (1506/1521)**	**98.4%–99.4%**

For the signs and symptoms population: excluding the unknown serostatus samples, the total PPA is 98.2 (111/113) (95%CI 93.8%–99.5%) and total NPA is 98.8% (883/894) (95% CI 97.8%–99.3%).

For the high-risk population: excluding the unknown serostatus samples for the high-risk prospective population, the total PPA is 96.3% (52/54) (95%CI 87.5%–99.0%) and total NPA is 99.3% (710/715) (95% CI 98.4%–99.7%).

All instrument systems demonstrated acceptable performance when compared with the reference assay. As expected, the agreement increased when the results were analyzed by the excluding 38 samples that did not fit into pre-determined serological status categories based on the patterns of the six HBV reference serological markers.

b. By HBV Serological Classification

1) Results on ADVIA Centaur XP

A total of 1814 samples including the 38 unknown serostatus samples were evaluated using the ADVIA Centaur Anti-HBe2 assay on the ADVIA Centaur XP and a reference aHBe assay for each sample classification (Table 17). The agreement and 95% CIs between the ADVIA Centaur Anti-HBe2 assay and a reference aHBe assay for each HBV classification are presented in the Table 18.

Table 17. ADVIA Centaur XP - Results of Prospective Population by HBV Serological Classification including Unknown Serostatus Samples

	Reference Assay-Reactive		Reference Assay-Nonreactive		
	ADVIA Centaur Anti-HBe2 Assay		ADVIA Centaur Anti-HBe2 Assay		
	Reactive	Nonreactive	Reactive	Nonreactive	Total
HBV classification	**N**	**N**	**N**	**N**	**N**
Acute	0	0	0	2	2
Chronic	33	0	2	23	58
Early Recovery	9	0	0	0	9
Recovery	15	0	0	0	15
Immune Natural Infection (Recovery)	106	4	0	0	110
Recovered	0	0	14	227	241
HBV Vaccine Response	0	0	0	597	597
Not previously infected	0	0	0	744	744
Unknown	0	9	1	28	38
Total	**163**	**13**	**17**	**1621**	**1814**

Table 18. ADVIA Centaur XP - Percent Agreement and Confidence Intervals in the Prospective Population by HBV Serological Classification including Unknown Serostatus samples

HBV classification	Positive Agreement		Negative Agreement	
	% (x/n)	95% CI	% (x/n)	95% CI
Acute	–	–	100% (2/2)	34.2%–100%
Chronic	100% (33/33)	89.6%–100%	92.0% (23/25)	75.0%–97.8%
Early Recovery	100% (9/9)	70.1%–100%	–	–
Recovery	100% (15/15)	79.6%–100%	–	–
Immune natural infection (Recovery)	96.4% (106/110)	91.0%–98.6%	–	–
Recovered	–	–	94.2% (227/241)	90.5%–96.5%
HBV Vaccine Response	–	–	100% (597/597)	99.4%–100%
Not previously infected	–	–	100% (744/744)	99.5%–100%
Unknown	0.0% (0/9)	0.0%–29.9%	96.6% (28/29)	82.8%–99.4%
Total	**92.6% (163/176)**	**87.8%–95.6%**	**99.0% (1621/1638)**	**98.3%–99.4%**

2) Results on ADVIA Centaur XPT

A total of 1697 samples were run using the ADVIA Centaur Anti-HBe2 assay on the ADVIA Centaur XPT and a reference aHBe assay for each HBV serological classification. Comparison of results is shown in Table 19 for all testing sites. The agreement and 95% CIs between the ADVIA Centaur Anti-HBe2 assay and a reference aHBe assay for each HBV classification are presented in the Table 20.

Table 19. ADVIA Centaur XPT - Results of Prospective Population by HBV Serological Classification including Unknown Serostatus Samples

HBV classification	Reference Assay-Reactive	Reference Assay-Nonreactive	Total
	ADVIA Centaur Anti-HBe2 Assay	ADVIA Centaur Anti-HBe2 Assay	

	Reactive	Nonreactive	Reactive	Nonreactive	
	N	N	N	N	N
Acute	0	0	0	2	2
Chronic	33	0	2	23	58
Early Recovery	9	0	0	0	9
Recovery	15	0	0	0	15
Immune Natural Infection (Recovery)	105	5	0	0	110
Recovered	0	0	11	228	239
HBV Vaccine Response	0	0	0	550	550
Not previously infected	0	0	0	676	676
Unknown	0	9	1	28	38
Total	**162**	**14**	**14**	**1507**	**1697**

Table 20. ADVIA Centaur XPT- Percent Agreement and Confidence Intervals in the Prospective Population by HBV Serological Classification including Unknown Serostatus samples

HBV classification	Positive Agreement		Negative Agreement	
	% (x/n)	95% CI	% (x/n)	95% CI
Acute	–	–	100% (2/2)	34.2%–100%
Chronic	100% (33/33)	89.6%–100%	92.0% (23/25)	75.0%–97.8%
Early Recovery	100% (9/9)	70.1%–100%	–	–
Recovery	100% (15/15)	79.6%–100%	–	–
Immune natural infection (Recovery)	95.5% (105/110)	91.0%–98.6%	–	–
Recovered	–	–	95.4% (228/239)	91.9%–97.4%
HBV Vaccine Response	–	–	100% (550/550)	99.3%–100%
Not previously infected	–	–	100% (676/676)	99.4%–100%

Unknown	0.0% (0/9)	0.0%–29.9%	96.6% (28/29)	82.8%–99.4%
Total	**92.0% (162/176)**	**87.1%–95.2%**	**99.0% (1507/1521)**	**98.5%–99.5%**

3) Results on ADVIA Centaur CP

A total of 1697 samples including pregnant women were run using the ADVIA Centaur Anti-HBe2 assay on the ADVIA Centaur CP and a reference aHBe assay for each HBV serological classification. A comparison of results in the prospective population by HBV serological classification is given below in the Table 21 with the unknown serostatus samples. The agreement and 95% CIs between the ADVIA Centaur Anti-HBe2 assay and a reference aHBe assay for each HBV classification are presented in the Table 22.

Table 21. ADVIA Centaur CP - Results of Prospective Population by HBV Serological Classification including Unknown Serostatus Samples

	Reference Assay-Reactive		**Reference Assay-Nonreactive**		
	ADVIA Centaur Anti-HBe2 Assay		**ADVIA Centaur Anti-HBe2 Assay**		
	Reactive	**Nonreactive**	**Reactive**	**Nonreactive**	**Total**
HBV classification	**N**	**N**	**N**	**N**	**N**
Acute	0	0	0	2	2
Chronic	33	0	2	23	58
Early Recovery	9	0	0	0	9
Recovery	15	0	0	0	15
Immune Natural Infection (Recovery)	107	3	0	0	110
Recovered	0	0	12	227	239
HBV Vaccine Response	0	0	0	550	550
Not previously infected	0	0	0	676	676
Unknown	0	9	1	28	38
Total	**164**	**12**	**15**	**1506**	**1697**

Table 22. ADVIA Centaur CP - Percent Agreement and Confidence Intervals in the Prospective Population by HBV Serological Classification including Unknown Serostatus samples

HBV classification	Positive Agreement		Negative Agreement	
	% (x/n)	95% CI	% (x/n)	95% CI
Acute	–	–	100% (2/2)	34.2%–100%
Chronic	100% (33/33)	89.6%–100%	92.0% (23/25)	75.0%–97.8%
Early Recovery	100% (9/9)	70.1%–100%	–	–
Recovery	100% (15/15)	79.6%–100%	–	–
Immune natural infection (Recovery)	97.3% (107/110)	92.3%–99.1%	–	–
Recovered	–	–	95.0% (227/239)	91.4%–97.1%
HBV Vaccine Response	–	–	100% (550/550)	99.3%–100%
Not previously infected	–	–	100% (676/676)	99.4%–00%
Unknown	0.0% (0/9)	0.0%–29.9%	96.6% (28/29)	82.8–99.4%
Total	**93.2% (164/176)**	**88.5%–96.1%**	**99.0% (1506/1521)**	**98.4%–99.4%**

The data presented from all three systems demonstrated acceptable performance of the Anti-HBe2 assay when compared with an FDA-approved reference assay

Pregnant Population

Serum samples were tested from 228 women with either signs and symptoms of HBV infection or with risk factors for HBV infection, who were in the first (90/228, 39.5%), second (71/228, 31.1%), or third trimester (67/228, 29.4%) of pregnancy.

The results were evaluated based on trimester (Table 23) and the PPA and NPA between the ADVIA Centaur Anti-HBe2 assay and the reference anti-HBe assay for each trimester is demonstrated in the Table 24.

Table 23. ADVIA Centaur XP, XPT and CP - Summary of Pregnant Population including Unknown Serostatus Samples

	Reference Assay - Reactive		Reference Assay - Nonreactive		Total
	ADVIA Centaur Anti-HBe2		ADVIA Centaur Anti-HBe2		
	Reactive	Nonreactive	Reactive	Nonreactive	
Trimester	**N**	**N**	**N**	**N**	**N**
First	0	0	0	90	90
Second	0	0	0	71	71
Third	2	1	0	64	67
Total	**2**	**1**	**0**	**225**	**228**

Table 24. ADVIA Centaur XP, XPT and CP - Percent Agreement and Confidence Intervals: Pregnant Population (all testing sites) including Unknown Serostatus Samples

	Positive Agreement		Negative Agreement	
Trimester	**% (x/n)**	**95% CI**	**% (x/n)**	**95% CI**
First	-	-	100% (90/90)	95.9%–100%
Second	-	-	100% (71/71)	94.9%–100%
Third	66.7% (2/3)	20.8%–93.9%	100% (64/64)	94.3%–100%
Total	**66.7% (2/3)**	**20.8%–93.9%**	**100% (225/225)**	**98.3%–100%**

These data indicate that the performance of the assay for detecting anti-HBe is acceptable in all trimesters of pregnancy on all three systems.

Pediatric Population

Pediatric (non-pregnant) samples were prospectively collected (N = 180). Due to the limited availability/occurrence of anti-HBe positive pediatric samples, the clinical study was supplemented with contrived samples to assess the positive percentage of agreement between ADVIA Centaur Anti-HBe2 and reference assay in pediatric population. The 63 contrived samples were prepared by spiking individual adult high positive samples into negative pediatric samples obtained from unique high-risk pediatric patients. The titer of the spiked samples ranged from 1.25 and >3.50 Index. The pediatric population was only tested on the ADVIA Centaur XP system due to volume limitations on those samples. The pediatric population analysis was stratified by two age groups: 2–12 years and 13–21 years. An evaluation of the performance of the assay on pediatric population (Table 25) and agreement and the 95% CI between the ADVIA Centaur Anti-HBe2 assay and a reference aHBe assay are presented (Table 26).

Table 25. ADVIA Centaur XP - Summary of Pediatric Populations (all testing sites)

Age Range (Years)	Reference Assay - Reactive		Reference Assay - Nonreactive		Total N
	ADVIA Centaur Anti-HBe2 Assay		ADVIA Centaur Anti-HBe2 Assay		
	Reactive	Nonreactive	Reactive	Nonreactive	
	N	N	N	N	
2-12	33	0	0	27	60
13-21	30	0	1	89	120
Total	**63**	**0**	**1**	**116**	**180**

Table 26. ADVIA Centaur XP - Percent Agreement and Confidence Intervals: Pediatric Population (all testing sites)

Age Range (Years)	Positive Agreement		Negative Agreement	
	% (x/n)	95% CI	% (x/n)	95% CI
2-12	100% (33/33)	89.6%–100%	100% (27/27)	87.5%–100%
13-21	100% (30/30)	88.6%–100%	98.9% (89/90)	94.0%–99.8%
Total	**100% (63/63)**	**94.3%–100%**	**99.1% (116/117)**	**95.3%–99.8%**

Comparison of the ADVIA Centaur XPT System and ADVIA Centaur XP System:

Because the ADVIA Centaur XP and ADVIA Centaur XPT systems are family members, the percent agreement between the instrument family members ADVIA Centaur XPT system and the ADVIA Centaur XP system was evaluated by testing 1697 (with unknown serostatus) and 1659 (without unknown serostatus) samples at three clinical testing sites. Each site used one ADVIA Centaur XPT system and one ADVIA Centaur XP system, and tested three lots of reagents. The samples included patients with general signs and symptoms of hepatitis or a high risk of HBV infection, including pregnant women. The results are given below in the Table 27 (unknown serostatus included) and Table 28 (unknown serostatus excluded)

Table 27. ADVIA Centaur XPT System versus ADVIA Centaur XP System with included Unknown Serostatus Samples

ADVIA Centaur XPT	ADVIA Centaur XP		
	Reactive	Nonreactive	Total

Reactive	175	1	176
Nonreactive	4	1517	1521
Total	**179**	**1518**	**1697**

The PPA was 97.8% (175/179) (95% CI 94.4% to 99.1%). The NPA was 99.9% (1517/1518) (95%CI 99.6% to 100%). These data indicate that the performance of the ADVIA Centaur Anti-HBe2 assay is equivalent on the ADVIA Centaur XP and ADVIA Centaur XPT instruments.

Table 28. ADVIA Centaur XPT System versus ADVIA Centaur XP System with excluded Unknown Serostatus samples

ADVIA Centaur XPT	**ADVIA Centaur XP**		
	Reactive	**Nonreactive**	**Total**
Reactive	174	1	175
Nonreactive	4	1480	1484
Total	**178**	**1481**	**1659**

The PPA was 97.8% (174/178) (95% CI 94.4% to 99.1%). The NPA was 99.9% (1480/1481) (95% CI 99.6% to 100%). These data indicate that the performance of the ADVIA Centaur Anti-HBe2 assay is equivalent on the ADVIA Centaur XP and ADVIA Centaur XPT instruments.

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 clinical study included three investigators. None of the clinical investigators were full-time or part-time employees of the sponsor and all three investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). 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 provision 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 Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The 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, ADVIA Centaur anti-HBe2 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.

B. Effectiveness Conclusions

The effectiveness of the ADVIA Centaur anti-HBe2 assay has been demonstrated by the sensitivity and specificity which has been comparable with the current commercially available FDA-approved anti-HBe assay among all populations tested. The results from both the non-clinical and clinical studies indicate that the ADVIA Centaur Anti-HBe2 assay is safe and effective for the in vitro qualitative detection of antibodies to the hepatitis B e antigen (Anti-HBe) in adults and pediatric serum and plasma (EDTA and Lithium Heparin).

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected on data collected in the clinical study conducted to support PMA approval as described above. The Hepatitis B Virus (HBV) represents a major global health concern. It causes a number of liver diseases, ranging from acute and chronic hepatitis to cirrhosis and primary liver cancer. Hepatitis B envelope (e) antigen (HBeAg) is found in the early phase of hepatitis B infection soon after hepatitis B surface antigen (HBsAg) becomes detectable. Serum levels of both antigens rise rapidly during the period of viral replication. The presence of HBeAg correlates with hepatitis B virus (HBV) infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and presence of viral DNA polymerase in serum. During recovery from acute hepatitis B, after HBeAg level declines and becomes undetectable, HBe antibody (anti-HBe) appears in the serum. Anti-HBe usually remains detectable for several years after recovery from acute infection. In HBV carriers and chronic hepatitis B patients, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or lack of HBV replication. Positive anti-HBe results usually indicate inactivity of the virus and low infectivity. Positive anti-HBe results usually indicate inactivity of the virus and low infectivity. Positive anti-HBe results in the presence of detectable HBV DNA in serum indicate active viral replication in these patients.

The benefit of the assay to detect antibodies to the HBeAg can be used to monitor the progress of hepatitis B viral infection. The assay will be used as an aid in the management of patients with chronic HBV infection undergoing antiviral therapy. Treatment with antiviral in timely manner may result improved morbidity and mortality in infected patients. The clinical studies suggest that patients will benefit from the assay.

The probable risks of the device are also based on the data collected in the clinical study conducted to support PMA approval as described above. 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 device. Risks of erroneously high results include improper patient management, such as treatment for hepatitis B with antiviral medication. Administration of antiviral medication has risks including toxicity and more rarely allergic reactions. Risks of erroneously low results include improper patient management, such as potentially missing and under-treating a patient who has hepatitis B infection. Under-treating a patient with hepatitis B infection whose clinical picture warrants antiviral treatment could result in the known sequelae of HBV infection and may result in higher morbidity and mortality in these patients. Under-treating hepatitis B in patients whose clinical picture otherwise warrants treatment will lead to continued symptoms, increases in all-cause mortality, liver disease-related complications and death, hepato-cellular carcinoma rates, and need for liver transplantation.

In conclusion, the clinical benefits outweigh the potential risks for the proposed assay, considering the mitigations of the risks provided in the premarket approval as well as general controls. The required premarket approval helps to ensure that errors will be uncommon and will facilitate accurate assay implementation and interpretation of results. The data supports that assay can aid in the management of patients with chronic HBV infection.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that for the claimed intended use the probably benefits outweigh the probably 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 Anti-HBe2 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 Anti-HBe2 assay, when compared to the FDA approved comparator, has a similar ability to detect the presence of anti-HBe 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 14, 2021

Given the workforce constraints associated with the 2019 SARS-CoV-2 public health emergency, a QSIT II post-market inspection is recommended in lieu of a preapproval inspection.

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.