SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:

Total antibodies to hepatitis B core antigen
Total antibodies to hepatitis B core antigen control material

Device Trade Name:

Elecsys® Anti-HBc Immunoassay, Elecsys® PreciControl Anti-HBc for use on the Elecsys® 2010 Immunoassay Analyzer

Applicant's Name and Address:

Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46256 USA

Date(s) of Panel Recommendation:

None

Premarket Approval Application (PMA) Number:

P100032

Date of FDA Notice of Approval:

June 27, 2011

Expedited:

Not Applicable

II. INDICATIONS FOR USE

Elecsys Anti-HBc Immunoassay

The Elecsys Anti-HBc immunoassay is for the *in vitro* qualitative determination of total antibodies to hepatitis B core antigen (anti-HBc) in human serum and plasma (lithium-heparin, sodium-citrate, K_2-EDTA) in adult patients with the symptoms of hepatitis or who may be at risk for hepatitis B (HBV) infection. The detection of total anti-HBc is indicative of a laboratory diagnosis for HBV infection. Further HBV serological marker testing is required to define the specific disease state. The Elecsys Anti-HBc immunoassay's performance has not been established for the monitoring of HBV disease or therapy.
The electrochemiluminescence immunoassay "ECLIA" is intended for use on the Elecsys 2010 immunoassay analyzer.

Elecsys Anti-HBc PreciControl

Elecsys PreciControl Anti-HBc is used for quality control of the Elecsys Anti-HBc immunoassay on the Elecsys 2010 immunoassay analyzer.

III. CONTRAINDICATIONS

Assay performance characteristics have not been established in patients under the age of 21, pregnant women, or in populations of immunocompromised or immunosuppressed patients.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions for the Elecsys Anti-HBc immunoassay and Elecsys PreciControl Anti-HBc are stated in the respective product labeling.

V. DEVICE DESCRIPTION

The assay is a competitive sandwich immunoassay based on the electrochemiluminescence principle. Total duration of testing time is 27 minutes.

1st incubation: 40 µl of sample is treated with a reducing agent.

2nd incubation: HBc antigen is added and a complex is formed with the anti-HBc antibodies in the sample.

3rd incubation: Biotinylated antibodies, ruthenium complex-labeled antibodies that recognize HBc Ag (**Tris (2,2' -bipyridyl)ruthenium(II)complex ($Ru(bpy)^{2/3+}$), and streptavidin-coated microparticles are added to the sample. The still-free binding sites on the HBc antigens are recognized and the complex becomes bound to the solid phase using the interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined automatically by the Elecsys 2010 software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by anti-HBc calibration.

Elecsys PreciControl Anti-HBc:

The Elecsys Anti-HBc Immunoassay uses the Elecsys PreciControl Anti-HBc for quality control. The controls, 1 (negative) and 2 (positive) contain IgG and IgM Anti-HBc antibodies in human serum and are used for monitoring the accuracy of the Elecsys Anti-HBc Immunoassay.

Kit Configuration and Components

Reagent:

The Elecsys Anti-HBc Immunoassay is composed of six reagents.

Component 1

Reagent M contains streptavidin-coated microparticles (beads) in a concentration of

0.72 mg/mL. The beads are suspended in 50 mmol/L of HEPES (4-(2-Hydroxyethyl)-1-piperazine-ethanesulfonic Acid) buffer with N-methylisothiazolone (0.01%), (MIT) and oxy-pyrion (0.10%) as preservatives. The reagent is provided ready-to-use and should be stored at 2-8°C upright.

Component 2
The R1 reagent contains recombinant hepatitis B core antigen (E. coli, rDNA), (45 ng/mL) in a phosphate buffer (pH 7.4). The reagent is preserved with 0.01% MIT and 0.10% oxy-pyrion. It also contains 0.12 µg/mL of monoclonal IgG antibody fragment and 80.6 µg/mL of polyclonal antibody to reduce interferences. This reagent is provided as ready-to-use and should be stored upright at 2-8°C.

Component 3
The R2 reagent contains purified biotinylated anti-HBc antibody (700 ng/mL) and ruthenylated anti-HBc antibody (200 ng/mL) (both mouse monoclonal) in a phosphate buffer, pH 7.4. Preservatives used are MIT at 0.01% and 0.10% oxy-pyrion. 3 mg/mL of polyclonal IgG antibody, 20 mg/mL of bovine serum plasma protein and 5 mg/mL of bovine serum protein are added as stabilizers. The reagent is ready-to-use and should be stored at 2-8°C upright.

Component 4
The R0 is the pre-treatment reagent that consists of dithiothreitol in a citrate buffer (pH 9.4). It functions as a reducing agent for the sample. R0 is buffered with sodium citrate, is ready-to-use and should be stored at 2-8°C upright.

Component 5
Cal 1 is the negative calibrator and consists of buffered (50 mmol/L HEPES) and preserved (0.4% Bronidox L) human serum which is negative for anti-HBc antibodies. The calibrator is non-reactive for HBsAg, anti-HCV and anti-HIV1 and 2 antibodies. It is provided ready-to-use and should be stored at 2-8°C.

Component 6
Cal 2 is the positive calibrator which consists of buffered (50 mmol/L HEPES) and preserved (0.4% Bronidox L) human serum negative for anti-HBc antibodies along with buffered and preserved human serum that is positive for anti-HBc antibodies (approximately 10 PE U/mL). The calibrator is non-reactive for HBsAg, anti-HCV and anti-HIV 1 and 2 antibodies. It is provided ready-to-use and should be stored at 2-8°C.

Elecsys PreciControl Anti-HBc

The Elecsys PreciControl Anti-HBc contains two reagents.

Component 1
PreciControl 1, PC 1 is the negative control and consists of two reagents, buffered (50 mmol/L HEPES) and preserved (0.4% Bronidox L) human serum which is negative for anti-HBc antibodies. The reagent is provided ready-to-use and should be stored at 2-8°C.

Component 2
PreciControl 2, PC 2 is the positive control which consists of two reagents, buffered (50 mmol/L HEPES) and preserved (0.4% Bronidox L) human serum negative for anti-HBc antibodies along with buffered and preserved human serum that is positive for anti-HBc antibodies (approximately 10 PE U/mL). The reagent is provided ready-to-use and should be stored at 2-8°C.

Calibrator

The Elecsys Calibrator 1 and Calibrator 2 are used to calibrate the Elecsys Anti-HBc test kit. The presence or absence of anti-HBc in the sample is determined by comparing the electrochemiluminescent signal in the reaction to the cut-off signal determined from an active Elecsys Anti-HBc calibration curve. If the electrochemiluminescent signal of the sample is less than or equal to the cut-off signal, the sample is considered reactive for Anti-HBc.

Interpretation of Results

Results are determined automatically by the Elecsys software by comparing the electrochemiluminescence signal obtained from the sample with the cut-off value obtained by the calibration of the Elecsys Anti-HBc. The result of a sample is given in the form of a cut-off index (COI—signal sample/signal cut-off) along with a result interpretation as follows:

COI > 1.1	Non-reactive (Negative)
1.1 ≥ COI > 0.9	Border (Borderline)
COI ≤ 0.9	Reactive (Positive)

Table 1: Clinical Interpretation of Anti-HBc Testing

Initial Elecsys Anti-HBc Assay			
COI	**Result**	**Interpretation of Results**	**Retest Procedure**
> 1.1	Non-reactive [a]	No antibodies to HBc were detected	No retest required
1.1 ≥ COI > 0.9	Border	Borderline zone (undetermined)	Retest in duplicate with the Elecsys Anti-HBc assay
≤ 0.9	Reactive	Antibodies to HBc detected	Follow CDC recommendations for supplemental testing

a) Note: A negative anti-HBc result can indicate that the patient is either susceptible to HBV infection due to no past exposure, or is immune to HBV due to vaccination.

Table 2: Clinical Interpretation of Repeat Anti-HBc Testing

Final Elecsys Anti-HBc Assay			
Initial Result COI	**Result after Retest (COI)**	**Final Results**	**Interpretation of Results**
> 1.1	No retest required	NON-REACTIVE [b]	Antibodies to HBc were not detected; does not exclude the possibility of exposure to HBV
1.1 ≥ COI > 0.9	If 2 of the 3 results have a COI > 1.0	NON-REACTIVE	Antibodies to HBc were not detected; does not exclude the possibility of exposure to HBV
	If 2 of the 3 results have a COI ≤ 1.0	REACTIVE	Presumptive evidence of antibodies to HBc. Follow CDC recommendations for supplemental testing.
≤ 0.9	No retest required	REACTIVE	Presumptive evidence of antibodies to HBc. Follow CDC recommendations for supplemental testing.

b) Note: A negative anti-HBc result can indicate that the patient is either susceptible to HBV infection due to no past exposure, or is immune to HBV due to vaccination.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently several FDA approved *in vitro* diagnostic tests for measuring antibodies (total with both IgG and IgM, and IgM only) to hepatitis B core antigen, which when used in conjunction with a patient's medical history, clinical examination, and other findings can be used for diagnostic purposes.

VII. MARKETING HISTORY

The Elecsys Anti-HBc Immunoassay has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. Failure of the test to perform as indicated or human error during performance of the test may lead to a false diagnosis and improper patient management.

Anti-HBc detects total antibodies to the hepatitis B core antigen. A false non-reactive result in a clinical setting can cause a physician to believe the patient's infection is not resolving when it is. Conversely, a false reactive result could lead the physician to believe the patient's infection is resolving when it is not. This could lead to missing a patient with chronic carrier status. To prevent these misdiagnoses, additional testing is often used, including the measurement of anti-hepatitis B e-antigen (Anti-HBe) and anti-hepatitis B surface antigen (Anti-HBsAg).

Incorrect results with an Anti-HBc assay (false positives or negatives) do not pose a public health problem because the assay alone does not provide information on chronic carrier status. Since chronic carriers are infectious for hepatitis B, they need to be tested periodically with an assay for hepatitis B surface antigen.

IX. SUMMARY OF PRECLINICAL STUDIES

All studies were performed using the Elecsys 2010 analyzer

A. Cutoff Determination

The establishment of the cut-off formula for the Elecsys 2010 analyzer was done by experimental design.

For the Elecsys Anti-HBc Immunoassay the cutoff is calculated from signal of the negative calibrator (Cal 1) and the positive calibrator (Cal 2) according to the following general formula:

$$(a) \times \text{Cal } 1 + (b) \times \text{Cal } 2 + c$$

The cut-off was established with internal studies measuring a panel of 240 samples from hospitalized subjects and from sample banks. Receiver Operator Curve (ROC) analysis was done to verify the cut-off and determine sensitivity and specificity.

The cut off for Elecsys Anti-HBc on Elecsys 2010 was verified by measuring in total 1563 samples including hospitalized subjects, seroconversion panels, and banked samples on the Elecsys 2010 analyzer.

B. Analytical Performance/Dilution Studies

For each production lot, the sensitivity at cut-off is determined by Quality Control (QC) during lot release. The analytical performance of the Elecsys Anti-HBc Immunoassay is calculated by reading off the concentration at the cut-off from the master calibrator curve. The concentration values for the master calibrator curve

were established via reference standardization.

The sensitivity at cut-off was calculated by reading off the concentration at the cutoff from the master calibrator curve (B) and the reference standard curve (A).

Study Description (A):
Reference material (Anti-HBc IgG Reference material 1982; lyophilized) obtained from Paul Ehrlich Institute, with a concentration of 100 PEI-U/mL, 0.5 mL, was pooled and diluted with non-reactive serum to a concentration of 6 U/mL. From this stock solution a dilution series with 7 dilution steps was generated from 0 to 2 PEI-U/mL. The 7 dilution steps were measured on Elecsys 2010 with three reagent lots. Sensitivity at cut-off was read of the reference standard curve.

Study Description (B):
The six master calibrators for Elecsys Anti-HBc were measured and concentration of cut-off was read off this calibrator curve. Four production lots were tested.

Additionally, the analytical sensitivity of the Elecsys Anti-HBc Immunoassay was evaluated by determining the Limit of Blank (LoB) and Limit of Detection (LoD) as described in CLSI guideline EP17-A. The limit of blank was determined to be 0.139 and 0.127 U/mL with two lots, and the limit of detection was determined to be 0.2023 and 0.1927 U/mL. The analytical sensitivity is conservatively set at ≤0.8 PEI U/mL.

C. Endogenous Interference

To evaluate the effect of elevated levels of hemoglobin, bilirubin, lipids (intralipid), biotin, total protein and human anti-mouse antibodies on the Elecsys Anti-HBc Immunoassay, interferent experiments were done with serum samples.

All samples were tested in triplicate for hemolysis, bilirubin, lipemia, biotin and total protein studies. Samples were tested in duplicate for the HAMA studies. The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the initial unspiked result. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

The results of this study demonstrated that samples containing hemolysate up to 0.8 g/dL, bilirubin up to 25 mg/dL, lipids up to 1000 mg/dL, biotin up to 30 ng/mL, total protein up to 10 g/dL, and HAMA up to 483 ng/mL should test accurately with the Elecsys Anti-HBc II Immunoassay.

D. Matrix Effects

Studies were conducted to verify the suitability of four types of blood collection tubes to be used with the Elecsys Anti-HBc assay. Samples were collected into matched serum and plasma collection tubes from 40 donors and assayed in triplicate on the Elecsys 2010 instrument. Forty matched pairs were collected in the evaluation of each: Serum/gel separator tubes, lithium heparin plasma, K_2-EDTA plasma and sodium citrate plasma. Samples were spiked with anti-HBc antibodies. For each set of comparisons, there were 10 samples negative for anti-HBc, 9 samples high-

negative for anti-HBc, 11 samples low-positive for anti-HBc and 10 samples positive for anti-HBc (serum gel separation experiments had 10 high-negative and 10 low-positive). These were defined as:

- Negative (targeted to approximately >1.3 COI)
- High negative (targeted to approximately 1.0-1.3 COI)
- Positive (targeted to approximately <0.7 COI)
- And low positive (targeted to approximately 0.7-1.0 COI)

The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the initial unspiked result. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

Statistical evaluations were done to analyze the cutoff index data for overall bias using orthogonal linear regression, which will reveal any relevant overall proportional bias.

The studies support the use of plasma collected using blood collection tubes containing the following anticoagulants:

- Lithium heparin
- K_2 EDTA
- Sodium citrate

The studies also support the use of serum separator tubes with the Elecsys Anti-HBc Immunoassay.

E. Drug Interference

A drug interference study was performed on the Elecsys 2010 immunoassay analyzer with 18 common therapeutic drugs. Each drug was spiked into a negative and a low positive sample. Samples were tested in triplicate and compared to an unspiked serum sample (reference) which was tested 9-fold. The spiked samples were evaluated at a concentration C1 ("x" times the maximum daily dosage). Mean COI, standard deviations and percent recoveries were calculated.

Each drug was found to not cause interference at the claimed concentrations. Since these studies were performed *in vitro*, they do not assess the potential interference when metabolized *in vivo*.

F. Carryover Study

On the 2010 analyzer, the use of disposable tips for sample pipetting and for reagent pipetting excludes any risk of carry over by design of test system. However, a study was performed to determine the extent of carryover in the instrument's measuring cell. First an anti-HBc negative sample was tested in triplicate. Next a reactive anti-Toxo IgG sample (which creates a high signal for toxo IgG at ≥ 2 million counts) was

tested. This was followed again by the respective anti-HBc negative sample, tested in triplicate.

The deviation of the first signal value of the negative sample after the high-signal generating sample was compared to the median signal of the triplicate measurements before testing the high-signal-generating sample. The procedure was repeated with a low positive anti-HBc sample followed again with a high Toxo-IgG sample and then followed with the low anti-HBc sample. The observed deviation in counts recovery met acceptance criteria of CV $\leq$ 7%. These studies demonstrate that there is no signal carry over with the Elecsys anti-HBc immunoassay.

G. High Dose Hook Effect

The Elecsys Anti-HBc II assay is not influenced by the high dose hook effect phenomenon because it is based on the competitive immunoassay principle. Therefore, no testing was performed.

H. Stability Studies

1. Sample Stability

Three studies were performed to verify the stability of patient samples using the Elecsys Anti-HBc immunoassay. The potential influence of storage of serum (n=12) and plasma (n=12) samples for 5 days at 2-8°C and 4 freeze/thaw cycles were evaluated. Serum (n=17) sample stability was evaluated at -20°C for 2 months (n=17). Tested were negative, high negative, low positive and positive samples run in triplicate.

For the storage at 2-8°C, samples were tested at time 0 (unstressed), 1, 2, 4 and 5 days. Time points tested for -20° were time 0 (unstressed) and 2 months. Freeze/thaw cycle samples were tested at time 0 (unstressed) and then after each freeze-thaw cycle (total of four cycles).

Recovery after storage for each test was calculated based on sample to cut-off index. The acceptance criteria for samples $\geq$ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the initial unstressed result. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

These studies indicate that serum and plasma patient samples may be stored for 5 days at 2-8 °C and can withstand 4 freeze/thaw cycles. Serum samples may be stored for 2 months at -20°C prior to testing by the Elecsys Anti-HBc assay.

2. Elecsys Anti-HBc Reagent Stability

i. Reagent Real-Time Stability

To assess the real-time stability, whole kit samples were chosen from three production lots. The kits were stored at the recommended storage temperature of

2-8°C, in a temperature-controlled area, for the duration of the ongoing stability studies. The measured intervals started with the production date, at least in the middle of the shelf life and one month after expiration.

Samples tested were human internal control samples (ICS) and PreciControl (PC). For real time stability, the lots were tested at 1, 10 and 14 months. Key stability parameters monitored for the Elecsys Anti-HBc assay were analytical sensitivity and results of internal control samples.

These studies to characterize the stability of the Anti-HBc assay confirm a shelf life of 14 months when stored at 2-8 °C. The product will be labeled with a shelf life of 13 months and the labeling will state that the reagent is stable, unopened at 2-8°C up to the stated expiration date.

ii. Reagent Temperature Stress Stability

Temperature stress stability studies were conducted to determine the effect of elevated temperature stress on Elecsys Anti-HBc immunoassay during transportation for one week at 35°C. A reagent kit was stressed for one week at 35°C. The stressed kit was then used to determine recoveries of 7 human serum samples and two internal PreciControls, tested in duplicate.

The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the result from the unstressed reagent. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

The results from the temperature stress studies indicated stability for the Elecsys Anti-HBc reagent for 1 week at 35°C.

iii. Reagent Stability After First Opening

Stability studies were performed to determine the time period in which the Elecsys Anti-HBc kits can be kept at 2-8°C once opened. A new reagent pack was opened and calibrated. Seven human serum and two PreciControls were tested in duplicate with the freshly opened reagent (unstressed) and then at 4, 8 and 9 weeks after storing at 2-8°C.

The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the result from the unstressed reagent. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

The reagent is stable for 9 weeks after opening, stored at 2-8°C. Eight weeks is claimed in the product labeling.

iv. On-Board Stability – Open Reagent Pack

Stability studies were performed to determine the time period in which Elecsys Anti-HBc immunoassay kits can be kept on-board the Elecsys 2010 analyzer once opened. A reagent kit was opened and calibrated and kept on-board the instrument for 5 weeks at 20°C (± 3°C). Seven human serum samples and two PreciControls were tested with the on-board reagent at time 0 and weeks 1, 2, 3, 4 and 5. For each testing point, the calibration had occurred seven days prior.

The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the result from the unstressed reagent. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

All acceptance criteria were met at each week tested. The reagent on-board stability is claimed for 4 weeks.

v. On-Board Stability – Open reagent Pack, On Board and Refrigerated

Stability studies were performed to determine the time period in which the Elecsys Anti-HBc Immunoassay kits can be stored in the refrigerator and alternatively on the Elecsys 2010 analyzer once opened.

An Elecsys Anti-HBc rack-pack was stored for 8 weeks in the refrigerator at 2 – 8°C and alternately on-board at 20°C (± 3°C) (up to 56 hours in total) to simulate on-board stress. Each week the reagent was checked with regard to stability of the weekly calibration.

A new reagent pack was opened and calibrated. Seven human sera samples and two PreciControls were tested in duplicates with the on-board reagent at time 0 and weeks 1, 2, 3, 4, 5, 6, 7, and 8. For each testing time point the calibration occurred seven days prior.

The acceptance criteria were fulfilled. The assay is labeled for storage of the reagent alternately in the refrigerator (2-8°C) up to 8 weeks and on-board the Elecsys 2010 analyzer for up to 56 hours in total.

3. Elecsys Anti-HBc Calibrator Stability Studies

i. On-Board Stability—Open Calibrators

Stability studies were performed to determine the time period in which the Elecsys Anti-HBc calibrators can be kept open on-board the Elecsys 2010 analyzer. A new Anti-HBc reagent pack was opened and calibrated, then stored at 2-8°C. Opened calibrators were stored at 32°C (the on-board condition of the Elecsys 2010 sample rotor disk for calibration). The calibrators were tested in duplicate in 6 one-hour intervals of incubation at 32°C. Recovery for each calibrator was calculated based on counts.

Acceptance criterion was 90-110% recovery of signal counts at ≥ 5 hours at 32°C. Criteria were met and the calibrators are labeled as stable open and on-board the Elecsys 2010 analyzer for 5 hours.

ii. Calibrator Stability after First Opening

Stability studies were performed to determine the time period in which the Elecsys Anti-HBc calibrators can be kept at 2-8°C. A new reagent pack was opened and calibrated, and then both reagent and calibrators were stored at 2-8°C for 9 weeks. The reagent was checked at 4, 8 and 9 weeks with new calibration. Seven human serum samples and two PreciControls were run in duplicate at time 0, 4, 8 and 9 weeks. The calibrator stability was determined by calculation of recovery of the samples compared to time 0.

The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the result from the original run. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

The acceptance criteria were met and the Elecsys Anti-HBc calibrators are labeled as stable for 8 weeks after first opening when stored at 2-8°C.

iii. Calibration Stability Studies

Calibration must be performed once per reagent lot using the Elecsys Anti-HBc Cal 1, Cal 2 and fresh reagent. Renewed calibration is recommended after 1 month with the same reagent lot and after 7 days with the same reagent kit.

Stability studies were performed to verify the claim that a lot calibration can be used for one month (28 days) with multiple reagent kits from the same lot (Lot Calibration Study) and that a calibration is stable for 7 days (Reagent Pack Calibration Study).

Lot Calibration Study

Two reagent lots were tested on three Elecsys 2010 analyzers. Two levels of PreciControl Anti-HBc, two negative, two borderline and two positive human serum samples were tested in duplicate. Fresh reagent was calibrated at day 0. On day 29, fresh reagent from the same lot was run to demonstrate the stability of the initial calibration.

The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the result from the original run. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

Acceptance criteria were met. The studies confirm calibration stability of one month with multiple reagent kits from the same lot. The product is labeled instructing a repeat of calibration at 28 days when using the same reagent lot.

Reagent Pack Calibration Study

An Elecsys Anti-HBc reagent pack was stored for 2 weeks in the refrigerator at 2-8°C and alternately on-board the Elecsys 2010 at 20°C (± 3°C) to simulate on-board stress. Each week the reagent was checked with regard to stability of the weekly calibration. Seven human serum samples (negative, borderline and positive) and two PreciControls were tested in duplicate with the on-board reagent at day 0 and after 1, and 2 weeks with weekly calibration. The acceptance criteria for samples ≥ 0.1 COI was a recovery within 60-140% COI for each individual sample and a mean recovery of 80-120% COI for all samples when compared to the result from the original run. The acceptance criteria for samples < 0.1 COI was a recovery of < 0.1 COI.

Acceptance criteria were met. The studies confirm calibration stability for 7 days on the Elecsys 2010 when using the same reagent kit.

4. **PreciControl Anti-HBc Studies**

i. PreciControl Real-Time Stability

To assess the real-time stability, whole kit samples were randomly selected from individual lots of finished product. The three randomly selected PreciControl kits were stored at the recommended storage temperature of 2-8°C. The test measurement intervals started with the production date of the last kit of reagent in the released kits, and continued, one intermediate time point, and t one month after expiration. Acceptance criteria were based on target ranges for each control and lot number (78-122% for PC1; 56-144% for PC2).

All acceptance criteria were met and the data support a shelf-life of 14 months. Stability for the Elecsys PreciControl Anti-HBc is claimed for 13 months.

ii. PreciControl Temperature Stress Stability

Temperature stress stability studies were conducted to demonstrate the stability of the PreciControl Anti-HBc during transportation for one week at 35°C. The stressed kit was compared to a PreciControl kit stored at 2-8°C (reference kit). The cut-off indices of the PreciControls were assessed in duplicate before and after storage. Acceptance criterion was recovery of 80-120% of unstressed material.

All acceptance criteria were met, demonstrating the Elecsys PreciControl Anti-HBc is stable for 1 week at 35°C.

iii. PreciControl Stability after First Opening

Stability studies were performed to determine the time period in which the Elecsys PreciControl Anti-HBc can be kept at 2-8°Conce opened. A new PreciControl kit was opened and tested, then stored at 2-8°C for 9 weeks. After 4, 8 and 9 weeks the stressed reagent was tested in duplicate along with unopened

PreciControl that had been stored at 2-8°C. Acceptance criterion was recovery of 80-120% of unopened material.

All acceptance criteria were met, demonstrating that the Elecsys PreciControl is stable after first opening when stored at 2-8°C for 9 weeks. Eight weeks stability is claimed.

iv. On-Board Stability—Open PreciControls

Stability studies were performed to determine the time period in which the Elecsys PreciControl Anti-HBc can be kept open on-board the Elecsys 2010 analyzer. A new Anti-HBc reagent pack and a new PreciControl kit were opened and tested. The reagent pack was then stored at 2-8°C and the opened PreciControls were stored at 32°C (upper limit of the ambient temperature on the analyzer). The PreciControls were tested in duplicate at 6 one-hour intervals. Acceptance criterion was 90-110% recovery of the signal counts at ≥ 5 hours.

All acceptance criteria was met at 6 hours on-board the Elecsys 2010. Stability of PreciControl Anti-HBc of up to 5 hours is claimed.

I. Antimicrobial Effectiveness Testing

Antimicrobial effectiveness testing (AET) has been performed according to United States Pharmacopoeia (USP) chapter <51>. Testing was performed with all reagents of Elecsys Anti-HBc and Elecsys PreciControl Anti-HBc.

One lot of each reagent was tested with a panel of microorganisms. All reagents were plated on appropriate media prior to inoculation, and non-inoculated controls were incubated in parallel and plated at each time point.

After inoculation, samples were plated on appropriate media at Day 0, Day 7, Day 14, and Day 28. To pass USP criteria, the bacterial concentration has to be reduced to 10% of the original inoculum by day 7, < 0.1 % of the original inoculum by day 14, and remain at or below this level until day 28. For yeast and molds, these are to remain at or below the original inoculum during the 28 day period.

Preservation of all reagents tested has been sufficient to pass USP.

In addition to these studies, each lot of components is checked for microbial contamination as part of the QC Release Testing Procedure. Microbial contaminants at a level which would compromise product performance would also fail quality assurance criteria listed in the product insert. No microbial outgrowth has been observed in components stored at elevated temperatures, relative to recommended 2–8° C storage, in previous accelerated stability studies.

J. Precision

Precision measurements were conducted to evaluate repeatability, and the intermediate precision of within laboratory precision according to CLSI guideline EP5-A2.

Internal precision

A six member precision panel consisting of 4 human sera (one moderate positive, one negative, one low positive (approximately 95 %), and one high negative (approximately 95 %) and two PreciControls (one positive and one negative) was measured in duplicate determinations in two runs per day for 12 days. The measurements were performed on one Elecsys 2010 analyzer, at one site, with one reagent lot performing weekly calibration, spanning at least two calibration cycles. Repeatability and within-laboratory precision was calculated according to EP5-A2.

Table 3: Repeatability

Sample	Mean (COI)	SD (COI)	CV (%)	n
Negative serum	1.84	0.065	3.5	48
High negative serum	1.03	0.016	1.5	48
Low positive serum	0.874	0.015	1.7	48
Positive serum	0.452	0.009	2.0	48
PC 1	1.60	0.022	1.4	48
PC 2	0.378	0.010	2.8	48

Table 4: Within-Laboratory Precision

Sample	Mean (COI)	SD (COI)	CV (%)	n
Negative serum	1.84	0.092	5.0	48
High negative serum	1.03	0.045	4.3	48
Low positive serum	0.874	0.041	4.7	48
Positive serum	0.452	0.028	6.1	48
PC 1	1.60	0.062	3.9	48
PC 2	0.378	0.042	11.2	48

External Precision

Precision was further evaluated incorporating between-run, between-day, between-lot and between-site variation. This study was done following CLSI EP5-A2 and CLSI EP15-A2 using three Elecsys 2010 instruments at three sites using three lots of reagent, with two lots at each site. Samples tested included PreciControl 1 and 2, four human serum pools near the cut-off and one moderately reactive human serum pool. Pools were tested in replicates of 3 in 2 runs per day for 5 days according to CLSI EP15-A2/EP 5-A2. The analysis of data was based on guidance from the CLSI documents EP5-A2 and EP15-A2. Data from all three reagent lots were combined to achieve SD and percent CV for repeatability, intermediate precision, between-day, between-lot, between-site and reproducibility. Results are summarized below.

Table 5: External Precision Data

Elecsys Anti-HBc reproducibility on the Elecsys 2010 Analyzer								
Sample		HS1	HS2	HS3	HS4	HS5	PC1	PC2
N		180	180	180	180	180	180	180
Mean	COI	1.178	1.094	0.916	0.825	0.611	1.666	0.379
Repeatability	SD	0.032	0.028	0.023	0.029	0.020	0.034	0.009
	%CV	2.7	2.6	2.5	3.5	3.3	2.0	2.5
Between-run	SD	0.027	0.023	0.019	0.015	0.013	0.038	0.011
	%CV	2.3	2.1	2.1	1.9	2.2	2.3	2.9
Between-day	SD	0.023	0.026	0.029	0.024	0.011	0.036	0.007
	%CV	1.9	2.4	3.1	2.9	1.7	2.1	2.0
Between-lot	SD	0.036	0.033	0.040	0.031	0.036	0.022	0.028
	%CV	3.1	3.0	4.4	3.8	5.8	1.3	7.4
Between-site	SD	0.000[c]	0.000[c]	0.000[c]	0.000[c]	0.000[c]	0.050	0.000[c]
	%CV	0.0	0.0	0.0	0.0	0.0	3.0	0.0
Reproducibility	SD	0.06	0.056	0.058	0.051	0.044	0.083	0.032
	%CV	5.1	5.1	6.3	6.2	7.3	5.0	8.5

c) SD of zero due to variance contributed by particular component was below stated significant figure

K. Analytical Specificity

A study was conducted to evaluate the Elecsys Anti-HBc Immunoassay for potential cross-reactivity for specimens from individuals with medical conditions unrelated to hepatitis B infection. The study was performed by testing 246 samples with 22 various known infectious diseases, vaccinations or medical conditions that could potentially interfere with hepatitis B core antibody testing. Of this group, 99 were white (40.2%), 33 black (13.4%), 4 Asian (1.6%), 1 Native American (0.4%), 3 other (1.2%) and 106 unknown (43.1%).

In this cohort, 206 samples (84%) were found to be non-reactive with both the reference and Elecsys Anti-HBc, assays and 35 samples (14%) were found to be reactive with both assays. No samples were reactive with the reference assay and non-reactive with the Elecsys assay, while 5 samples (2%) were reactive with the Elecsys assay and non-reactive with the reference assay.

The study demonstrated a negative percent agreement between Elecsys and the reference anti-HBc antibody assays of 97.63% (206/211) with a 95th percentile confidence interval of 94.56-99.23%. The overall negative and positive percent agreement was 97.97% (241/246) with a 95th percentile confidence interval of 95.32-99.34%.

Table 6: Analytical Specificity in Subjects with Other Known Conditions

Reference Assay	**Reactive**		**Non-Reactive**		**Total samples**
Elecsys Anti-HBc Assay	**Reactive**	**Non-Reactive**	**Reactive**	**Non-Reactive**	**n**
Anti-nuclear antibody (ANA)	0	0	0	15	15
Cytomegalovirus (anti-CMV positive)	2	0	0	10	12
Epstein Barr virus (anti-EBV positive)	0	0	0	11	11
Hepatitis A (anti-HAV positive)	0	0	0	9	9
HAV Vaccination	0	0	0	6	6
Hepatitis C (anti-HCV positive)	3	0	1[1]	8	12
Hepatitis D (anti-HDV positive)	5	0	0	0	5
Hepatitis E (anti-HEV positive)	6	0	2[1]	3	11
Human immunodeficiency virus (anti-HIV-1 positive)	5	0	1[1]	3	9
Herpes Simplex (HSV) IgG	0	0	0	9	9
Human T Cell Lymphotropic Virus (HTLV)	2	0	1[1]	9	12
Non-viral liver disease	1	0	0	37	38
Parvovirus (B_{19}) infection	0	0	0	9	9
Rheumatoid factor	0	0	0	11	11
Rubella	0	0	0	10	10
Syphilis (T. *pallidum*)	2	0	0	9	11
Toxoplasmosis IgG positive	2	0	0	6	8
Influenza Vaccine recipients	0	0	0	10	10
HBV Vaccination	0	0	0	7	7
E. *coli* infection	6	0	0	6	12
Pregnancy	0	0	0	11	11
Varicella Zoster (Anti-VZV)	1	0	0	7	8
Total	35	0	5	206	246

Samples that tested reactive for anti-HBc by the reference method were not further evaluated to establish the true hepatitis B infection status.

The potential for cross-reactivity between anti-HDV reactive and anti-HBc non-reactive samples has not been established.

[1] A total of five discrepant results were observed with the Elecsys Anti-HBc Immunoassay: HCV (1/12), HEV (2/11), HTLV I/II (1/12), HIV (1/9)

L. Seroconversion Analysis

Seroconversion sensitivity of the Elecsys anti-HBc Immunoassay was demonstrated by testing seven commercially sourced seroconversion panels in comparison to that of a reference anti-HBc assay. The panels consisted of a total of 78 specimens which were run using the Elecsys Anti-HBc and the reference anti-HBc immunoassays. The sources of the panels were ZeptoMetrix (ZPT) and SeraCare/bbi (SC/bbi). Demographics and medical history on most of these subjects were not supplied.

The comparison of the seroconversion detection between the assays in terms of days is summarized in the table below.

Table 7: Results for Days of Evidence of anti-HBc Seroconversion for the Elecsys anti-HBc Compared to the Reference Assay

Panel ID	Days to change in reactivity of Anti-HBc IgM results				Difference in Days to Elecsys Anti-HBc Reactivity (Reference-Elecsys)[a]
	Reference Anti-HBc		Elecsys Anti-HBc		
	NR[b]	RX[c]	NR	RX	
11024	54	NC[d]	54	NC	N/A
6278	37	41	33	37	4
6281	36	41	36	41	0
9072	159	NC	159	NC	N/A
PHM933	16	144	16	144	0
PHM934	14	84	14	84	0
PHM935B	--[e]	128	--[e]	128	0

a. The dates of the first reactive test results were compared in the reference assay and the Elecsys Anti-HBc assay. If the first reactive test result occurred on the same day, then the difference is 0; if the Elecsys Anti-HBc assay had an earlier date, then the difference is positive; if the Elecsys Anti-HBc assay had a later date, then the difference is negative.
b. NR = non-reactive
c. RX = reactive
d. NC = no conversion
e. All bleeds were positive for anti-HBc

The Elecsys Anti-HBc was reactive in the same bleed as the reference assay in 4 of the 7 panels tested. The Elecsys Anti-HBc assay was reactive earlier than the reference assay in one panel. Seroconversion never occurred in either assay in 2 panels.

X. SUMMARY OF PRIMARY CLINICAL STUDY

To evaluate the Elecsys Anti-HBc assay's ability to detect antibodies to HBc in a group of individuals that would normally be tested in a clinical situation, a multi-center prospective study was conducted to evaluate the clinical performance on the Elecsys 2010 analyzer.

The study population included individuals with specific risks or history associated with hepatitis B infection. Medical/clinical risks included a history of transplants or blood transfusions and/or

clotting factors, HIV infection or other immunodeficiency diseases, hemodialysis patients, prenatal exposure to HBV and a family history of any hepatitis. Occupational risks included healthcare workers, tattoo artists, morticians and individuals with a history of incarceration. Sexual risks included individuals with multiple sex partners, individuals with a history of sexual contact with partners with STDs (including HIV), male-on-male sex partners and commercial sex workers. Behavioral risks included IV drug use, cocaine users who ingested the drug through shared straws, and individuals with tattoo or body piercings.

A total of 1,526 prospective subjects were recruited for the diagnostic accuracy analysis and were divided into two groups, Asymptomatic at Risk (n=959, 63%) and Symptomatic at Risk (n=567, 37%) populations. The Asymptomatic at Risk population was required to have no clinical symptoms of liver disease. The Symptomatic at Risk group was required to have laboratory data or histological findings suggestive for hepatitis infection including jaundice, discoloration of urine or stool, non-specific GI symptoms such as nausea or vomiting, flu-like symptoms, elevated ALT, AST or bilirubin, cryoglobulinemia, lymphoma, autoimmune thyroiditis, renal disease, dermatologic conditions such as lichen plannus or porphyria cutanea tarda, and histological evidence of liver disease (if available). The signs and symptoms population must also belong to one of the listed at-risk groups for HBV.

The prospective samples for these cohorts were collected from multiple US sites including Miami, Coconut Creek and Ft. Lauderdale, Florida; Los Angeles, CA; Newark, NJ; and Atlanta, GA. Final analysis included 1,526 subjects with 72% male and 28% female subjects. Overall, 47.9% of patients were black, 0.66% Native American, 0.33% Asian, 45.8% white (Hispanic and non-Hispanic), 0.26% Pacific Islander with 1.18% defined as other and 3.87% classified as unknown. Ages for both cohorts ranged from 21 to 79 with a median of 43 years.

Table 8: Demographic Summary of Race of Subject by Gender and Age in the Clinical Cohort (Asymptomatic and Symptomatic)

Age	Gender	Black	White	Asian	Native American	Pacific Islander	Other	Unknown	Total
21-30	Male	27	84	1	1	0	5	32	150
	Female	25	90	1	0	1	0	6	123
31-40	Male	90	112	1	1	0	3	7	214
	Female	31	56	0	1	0	3	3	94
41-50	Male	253	166	0	3	2	5	2	431
	Female	80	44	0	1	0	0	2	127
51-60	Male	163	82	2	2	1	0	5	255
	Female	41	31	0	0	0	1	0	73
61-70	Male	17	20	0	0	0	1	2	40
	Female	2	8	0	1	0	0	0	11
71-80	Male	1	4	0	0	0	0	0	5
	Female	1	2	0	0	0	0	0	3
Totals	Male	551	468	4	7	3	14	48	1095
	Female	180	231	1	3	1	4	11	431
	All	731	699	5	10	4	18	59	1526

Table 9: Demographic Summary of Overall Specimen Population by Age and Gender in an Asymptomatic At Risk Population

Population		Elecsys Anti-HBc Assay		
Age	**Gender**	**Positive n (percent of total)**	**Negative n (percent of total)**	**Total**
21 - 30	Male	9 (11)	73 (89)	82
	Female	6 (7)	76 (93)	82
31 – 40	Male	51 (34)	100 (66)	151
	Female	12 (20)	49 (80)	61
41 – 50	Male	126 (45)	151 (55)	277
	Female	29 (35)	53 (65)	82
51 - 60	Male	72 (48)	78 (52)	150
	Female	22 (48)	24 (52)	46
61 – 70	Male	6 (35)	11 (65)	17
	Female	3 (50)	3 (50)	6
71 - 80	Male	2 (50)	2 (50)	4
	Female	0 (0)	1 (100)	1
Totals	Male	266 (39)	415 (61)	681
	Female	72 (26)	206 (74)	278
	All	338 (35)	621 (65)	959

Table 10: Demographic Summary of Overall Specimen Population by Age and Gender in a Symptomatic At Risk Population

Population		Elecsys Anti-HBc Assay		
Age	**Gender**	**Positive n (percent of total)**	**Negative n (percent of total)**	**Total**
21 - 30	Male	32 (47)	36 (53)	68
	Female	9 (22)	32 (78)	41
31 – 40	Male	15 (24)	48 (76)	63
	Female	9 (27)	24 (73)	33
41 – 50	Male	50 (32)	104 (68)	154
	Female	21 (47)	24 (53)	45
51 - 60	Male	49 (47)	56 (53)	105
	Female	9 (33)	18 (67)	27
61 – 70	Male	14 (61)	9 (39)	23
	Female	3 (60)	2 (40)	5
71 - 80	Male	1 (100)	0 (0)	1
	Female	0 (0)	2 (100)	2
Totals	Male	161 (39)	253 (61)	414
	Female	51 (33)	102 (67)	153
	All	212 (37)	355 (63)	567

Specimen Classification:

Tests from an HBV marker assay panel were run on each clinical specimen to determine a single time-point serological diagnosis of HBV disease status. All assays used were FDA approved/cleared. The Elecsys HBsAg and Anti-HBs Immunoassays on the 2010 or E170 served as FDA approved reference assays. Further reference testing was conducted with the Abbott AxSYM CORE 2.0 (anti-HBc) and CORE M 2.0 (anti-HBc IgM) assays and the DiaSorin ETI-AB-EBK Plus (anti-HBe) and ETI-EBK Plus (HBeAg) assays. These assays were performed according to the manufacturer's instructions.

The interpretation algorithm for the various HBV classifications based on the serological profiles recorded in the database is shown in the table below:

Table 11: Serological Classification by FDA-Approved HBV Panel

	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc	Anti-HBe	Anti-HBs
Acute	(+)	(+)	(-)	(-)	(-)	(-)
Acute	(+)	(+) or (-)	eq	(+)	(+)	(-)
Acute	(+)	(+)	(+)	(+)	(-), (+), nd/qns	(-)
Acute	(+)	(-)	(+)	(+)	(+)	(-)
Acute	(+)	qns	(+)	(+)	(+)	(-)
Acute	(+)	(+)	(+)	(+)	(-)	eq
Acute (Late)	(+)	(-)	(+)	(+)	(+)	(+)
Chronic	(+) >6 mo.					
Chronic	(+) >6 mo.	(-)	(-)	(+)	(+), eq, (+)	(-)
Chronic	(+) >6 mo.	(+)	eq	(+)	(-)	(-)
Chronic	(+)	(+)	(-)	(+)	(-)	(-)
Chronic	(+)	(-)	(-)	(+)	(+), eq, (+)	(-)
Chronic	(+)	(+)	(+)	(+)	(-)	(+)

	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc	Anti-HBe	Anti-HBs
Early Recovery	(-)	(-)	eq	(+)	(+)	(+) or eq
Early Recovery	(-)	(-)	(+)	(+)	(+)	(+)
Early Recovery	(-)	(-)	(-)	(+)	(+), eq, (-). qns	(-)
Recovery	(-)	(-)	(-)	(+)	(+)	(+) or eq
Recovery	(-)	(-)	(-)	(+)	eq	(+)
Recovery	(-)	(-)	(-)	(-)	(+)	(+)
Recovered or Immune Due to Natural Infection	(-)	(-)	(-)	(+)	(-)	(+) or eq
HBV Vaccine Response	(-)	(-)	(-)	(-)	(-)	(+)
HBV Vaccine Response (?)	(-)	(-)	(-)	(-)	(-)	eq
Not Previously Infected	(-)	(-)	(-)	(-)	(-)	(-)
Not Previously Infected	rr uncnf	(-)	(-)	(-)	(-)	(-)
Not Interpretable	(+)	(+)	nd	(+)	(+) or (-)	(-)
Not Interpretable	(+)	(-)	eq	(+)	(-)	(+)
Not Interpretable	(-)	(-)	(-)	(-)	(+)	(-)
Not Interpretable	(-)	(-)	(-)	(+)	qns	(+)
Not Interpretable	(-)	(+)	(-)	(-)	(-)	(+) or (-)
Not Interpretable	qns	(-)	(-)	(-)	(-)	(-)

nd = not detected
eq = equivocal or indeterminate or borderline
rr uncnf = repeatedly reactive; did not confirm
qns = incomplete or unconfirmed

Sample Classification Results

Samples from the 2 cohorts were classified as shown below. Elecsys Anti-HBc results were not used in this classification. Those doing the categorization were blinded to those values.

Table 12: HBV Classification by Serology in Asymptomatic at Risk Cohort

HBV Classification	Total	Percent
Acute	8	0.83
Chronic	28	2.92
Early Recovery	62	6.47
Recovery	139	14.49
Recovered	97	10.11
HBV Vaccination	189	19.71
Not Previously Infected	432	45.05
Not Interpretable	4	0.42
Total	959	100.00

Table 13: HBV Classification by Serology in Symptomatic at Risk Cohort

HBV Classification	Total	Percent
Acute	48	8.47
Chronic	10	1.76
Early Recovery	40	7.05
Recovery	70	12.35
Recovered	34	6.00
HBV Vaccination	135	23.81
Not Previously Infected	225	39.68
Not Interpretable	5	0.88
Total	567	100.00

Results by Specimen Classification

Samples were then run on the Elecsys 2010 analyzer using the Elecsys Anti-HBc Immunoassay, and on the reference analyzer using the reference anti-HBc assay. Tables 14 and 16 below show the results of the two assays in comparison to the subject classification, while Tables 15 and 17 show the positive and negative agreement.

Table 14 summarizes the results of the two assays in comparison to the HBV classification in the asymptomatic at risk cohort. In this group 13 samples (1.4%) were negative by the reference assay and positive by the Elecsys Anti-HBc Immunoassay. Additionally, 8 samples (0.8%) were positive by the reference assay and negative by the Elecsys Anti-HBc Immunoassay.

Table 14: Comparison of Elecsys on E2010 to the Reference Assay Results by HBV Classification in the Asymptomatic At Risk Cohort

HBV Classification	Reference Results				Total
	+		-		
	Elecsys Anti-HBc Test Result				
	+	-	+	-	
Acute	7	0	0	1	8
Chronic	27	1	0	0	28
Early Recovery	61	1	0	0	62
Recovery	138	0	1	0	139
Recovered	91	6	0	0	97
HBV Vaccination	0	0	6	183	189
Not Previously Infected	0	0	6	426	432
Not Interpretable	1	0	0	3	4
Total	325	8	13	613	959

The following table summarizes the percent agreement between the Elecsys Anti-HBc and the reference assays for each specimen classification, and provides the upper and lower 95% exact confidence bounds. The percent positive agreement among the asymptomatic at risk subjects was 97.60 % (325/333) and the percent negative agreement was 97.92 % (613/626).

Table 15: Positive and Negative Percent Agreement in the Asymptomatic at Risk Population

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	100.00 (7/7)	59.04 to 100.00	100.00 (1/1)	2.50 to 100.00
Chronic	96.43 (27/28)	81.65 to 99.91	0.00 (0/0)	0.00 to 100.00
Early Recovery	98.39 (61/62)	91.34 to 99.96	0.00 (0/0)	0.00 to 100.00
Recovery	100.00 (138/138)	97.36 to 100.00	0.00 (0/1)	0.00 to 97.50
Recovered	93.81 (91/97)	87.02 to 97.70	0.00 (0/0)	0.00 to 100.00
HBV Vaccination	0.00 (0/0)	0.00 to 100.00	96.83 (183/189)	93.22 to 98.83
Not Previously Infected	0.00 (0/0)	0.00 to 100.00	98.61 (426/432)	97.00 to 99.49
Not Interpretable	100.00 (1/1)	2.50 to 100.00	100.00 (3/3)	29.24 to100.00
Total	97.60 (325/333)	95.32 to 98.96	97.92 (613/626)	96.47 to 98.89

The following table summarizes the results of the two assays in comparison to the HBV classification in the symptomatic at risk cohort. In this group, 11 samples (1.9%) were negative by the reference assay and positive by the Elecsys Anti-HBc Immunoassay. Additionally, 4 (0.7%) samples were positive by the reference assay and negative by the Elecsys Anti-HBc Immunoassay.

Table 16: Comparison of Elecsys on the E2010 to the Reference Assay Results by HBV Classification in the Symptomatic At Risk Cohort

HBV Classification	Reference Results				Total
	+		-		
	Elecsys Anti-HBc Test Result				
	+	-	+	-	
Acute	48	0	0	0	48
Chronic	9	1	0	0	10
Early Recovery	38	2	0	0	40
Recovery	70	0	0	0	70
Recovered	33	1	0	0	34
HBV Vaccination	0	0	6	129	135
Not Previously Infected	0	0	4	221	225
Not Interpretable	3	0	1	1	5
Total	201	4	11	351	567

The following table summarizes the percent agreement between the Elecsys Anti-HBc Immunoassay and the reference assay for each specimen classification, and provides the upper and lower 95% exact confidence bounds. As shown, among the symptomatic at risk subjects, the positive and negative percent agreements were 98.05% (201/205) and 96.96 (351/362), respectively.

Table 17: Percent Agreement between Elecsys (E2010) and anti-HBc Reference Assay for each Specimen Classification: Symptomatic At Risk

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	100.00 (48/48)	93.60 to 100.00	0.00 (0/0)	0.00 to 100.00
Chronic	90.00 (9/10)	55.50 to 99.75	0.00 (0/0)	0.00 to 100.00
Early Recovery	95.00 (38/40)	83.08 to 99.39	0.00 (0/0)	0.00 to 100.00
Recovery	100.00 (70/70)	94.87 to 100.00	0.00 (0/0)	0.00 to 100.00
Recovered	97.06 (33/34)	84.67 to 99.93	0.00 (0/0)	0.00 to 100.00
HBV Vaccination	0.00 (0/0)	0.00 to 100.00	95.56 (129/135)	90.58 to 98.35
Not Previously Infected	0.00 (0/0)	0.00 to 100.00	98.22 (221/225)	95.51 to 99.51
Not Interpretable	100.00 (3/3)	29.24 to 100.00	50.00 (1/2)	1.26 to 98.74
Total	98.05 (201/205)	95.08 to 99.47	96.96 (351/362)	94.63 to 98.47

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the FDA 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 adverse effects of the device are based on data collected in a clinical studies conducted to support PMA approval as described above. As a diagnostic test, the Elecsys Anti-HBc Immunoassay for use on the Elecsys 2010 Immunoassay Analyzer involves removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood is drawn.

B. **Effectiveness Conclusions**

- The Elecsys Anti-HBc Immunoassay performance is acceptable when testing in serum, gel separator tubes and lithium heparin, K_2-EDTA and sodium citrate plasma.
- There are no issues with endogenous interferents at physiological levels, or with commonly administered medications.
- Samples are stable when refrigerated for 5 days (2-8°C) or frozen for 2 months (-20°C). They can also withstand 4 freeze/thaw cycles.
- The Elecsys Anti-HBc reagent demonstrates stability of 13 months when stored at 2-8°C. It can withstand stress at 35°C for one week. It is stable for 8 weeks after opening when stored at 2-8°C. It is stable on-board the Elecsys 2010 for 4 weeks.
- The Elecsys Anti-HBc calibrators are stable on-board the Elecsys 2010 for 5 hours. The calibrators are stable for 8 weeks when stored at 2-8°C. Calibration is stable for one month when using multiple kits from the same reagent lot and for 7 days when using the same reagent kit.
- The Elecsys PreciControl Anti-HBc is stable for 13 months when stored at 2-8°C. It can withstand stress at 35°C for one week. It is stable for 8 weeks after opening when stored at 2-8°C, and is stable on-board the Elecsys 2010 for 5 hours.
- The preservative systems that the Elecsys Anti-HBc Immunoassay reagents and PreciControls contain have been shown to meet USP Chapter 51.
- The Elecsys Anti-HBc Immunoassay demonstrated precision estimates (CVs) of < 4% for repeatability, < 3% between-run, < 4% between-day, < 6% between-lot, < 3% between-site and < 9% for reproducibility.

C. **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 submitted clinical studies have shown that the Elecsys Anti-HBc immunoassay, when compared to reference clinical laboratory procedures, has a similar ability to detect the presence of antibodies to hepatitis B core antigen in specimens from individuals infected with HBV (state of infection or associated disease not determined). The rate of false positivity and false negativity are within acceptable limits compared to the reference assay. It has been shown that the device has no demonstrable cross-reactivity with the majority of viruses or organisms that may cause clinical hepatitis. Therefore, this device should benefit the physician in the diagnosis of HBV.

XIII. CDRH DECISION

CDRH issued an approval order on June 27, 2011.

The applicant's manufacturing facilities were inspected on January 21, 2011, February 10, 2011, and February 15, 2011 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.