

SUMMARY OF SAFETY AND EFFECTIVENESS

1. General Information

- 1.1. Name and Address of Applicant: Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, IN 46256 USA
- 1.2. Device Trade Name(s): Elecsys[®] Anti-HBs Immunoassay
Elecsys[®] Anti-HBs PreciControl
- 1.3. Device Generic Names: Antibody to hepatitis B surface antigen (anti-HBs) assay
Antibody to hepatitis B surface antigen (anti-HBs) control
- 1.4. PMA Number: P010054
- 1.5. Date of Good Manufacturing Inspection: July 20, 2000
- 1.6. Date of Notice of Approval to Applicant: February 28, 2002

2. Indications for Use

2.1. Elecsys[®] Anti-HBs Immunoassay

For the in vitro qualitative determination of total antibodies to the hepatitis B surface antigen (HBsAg) in human serum and plasma (EDTA). The electrochemiluminescence immunoassay "ECLIA" is intended for use on the Roche Elecsys 2010 immunoassay analyzer.

Assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

The detection of anti-HBs is indicative of laboratory diagnosis of seroconversion from hepatitis B virus (HBV) infection.

3. Device Description

3.1. Principle of Device Methodology

3.1.1. The Elecsys[®] Anti-HBs Immunoassay is used for the qualitative measurement of antibodies to hepatitis B surface antigen (HBsAg) in human serum and plasma (EDTA). The assay is based on the principles of electrochemiluminescence.

In the first incubation, anti-HBs in the sample, a biotinylated HBsAg and HBsAg labeled with a ruthenium complex react to form a “sandwich” complex. After the addition of streptavidin-coated microparticles the complex becomes bound to the solid phase via interaction of biotin and streptavidin. After incubation 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 a buffer. Application of a voltage to the electrode then induces chemiluminescent emission that is measured by a photomultiplier. Results are determined automatically by the Elecsys software by comparing the electrochemiluminescence signal obtained from the sample with the cutoff value previously obtained by anti-HBs calibration. The total duration of the assay is 18 minutes.

3.1.2. The Elecsys PreciControl Anti-HBs contains human serum in the negative and positive concentration range that are used for monitoring the accuracy of Elecsys Anti-HBs Immunoassay.

3.2. Kit Configuration and Component

3.2.1. The Elecsys[®] Anti-HBs Immunoassay is composed of five reagents:

- The M reagent consists of streptavidin coated microparticles (“beads”) in HEPES (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid) buffer with preservative.
- The R1 reagent, HBsAg-biotin, consists of purified biotinylated HBs antigen (ad/ay) in a MES (2-morpholino-ethanesulfonic acid) buffer solution with preservative.
- The R2 reagent, HBsAg~ Ru(bpy)₃²⁺ consists of purified human HBs-antigen (ad/ay) labeled with ruthenium complex in a MES (2-morpholino-ethanesulfonic acid) buffer solution with preservative.
- Cal 1, Negative Calibrator, consists of Anti-HBs (human, 4-15 IU/L) in human serum, non-reactive for HBsAg, anti-HCV, anti-HIV 1+2, with preservative.
- Cal 2, Positive Calibrator, consists of anti-HBs (human, 350-600 IU/L) in human serum, non-reactive for HBsAg, anti-HCV, anti-HIV 1+2, with preservative.

3.2.2. The Elecsys PreciControl Anti-HBs contains two reagents

- PreciControl 1, PC Anti-HBs 1, consists of human anti-HBs (≤ 4 IU/L) in human serum, non-reactive for anti-HCV, anti-HIV 1+2, with preservative.
- PreciControl 2, PC Anti-HBs 2, consists of human anti-HBs (approx. 100 IU/L) in human serum, non-reactive for anti-HBs, anti-HCV, anti-HIV 1+2, with preservative.

4. Contraindications

There are no known contraindications for the Elecsys[®] HBsAg Immunoassay.

5. Warnings and Precautions

Warnings and precautions are stated in the attached product labeling.

6. Alternative Practices and Procedures

There are currently several FDA approved and licensed in vitro diagnostic tests for serological markers of hepatitis B virus (HBV) infection which when used in conjunction with a patient's medical history, clinical examination, and other findings can be used for diagnostic purposes.

7. Prior Marketing History

The Elecsys[®] Anti-HBs Immunoassay and Elecsys PreciControl Anti-HBs has been marketed worldwide since 1998. The following list represents the countries where these devices have been marketed.

Argentina	Asia Pacific	Athens	Australia	Austria	Bahrain
Belarus	Belgium	Bosnia & Herzegovina	Brazil	Brazil	Budapest
Bulgaria	Canada	Cyprus	Egypt	Estonia	France
Germany	Hong Kong	Hungary	Iceland	Israel	Italy
Japan	Johannesburg	Jordan	Korea	Lebanon	Libyan Arab Jamahiriya
Lima	Lithuania	Luxembourg	Malta	Marokko	Mexico
Montevideo	Morocco	Moscow	Netherlands	New Zealand	Nigeria
Oman	Polska	Prague	Quito	Romania	Saudi Arabia
Slovenia	Spain	Spain	Switzerland	Syrian Arab Republic	Thailand
Tunisia	Turkey	UK	United Arab Emirates	Uruguay	Venezuela

The device has not been withdrawn from marketing in any country for reasons relating to the safety and effectiveness of the device.

8. Potential Adverse Effects of the Device on Health

As an *in vitro* diagnostic, there is no direct adverse effect of the Elecsys Anti-HBs Immunoassay test system on the health of the patient.

The possibility of erroneous test results due to test malfunctions or operator errors exists. A false non-reactive result cannot be considered a patient or public health concern, as the patient would either unnecessarily receive a vaccine, vaccine booster, hyperimmune globulin, or be considered not to have recovered from an HBV infection when they have.

A false reactive assay may be a patient or a public health concern because the patient is considered to be immune to natural HBV infection or that the patient was successfully vaccinated. In this case, the risk is that the patient would not receive a vaccine, vaccine booster, hyperimmune globulin, and would be at higher risk of infection if exposed to HBV. Once exposed, the risk of this patient spreading infection to uninfected or non-immune members of the community increases.

The risk of incorrect test results is inherent with all *in vitro* diagnostic products. Therefore, the above potential risks are not unusual in the laboratory setting. Appropriate warnings for each of these risks are contained in the labeling and package insert instructions. Standard good laboratory practices are considered sufficient to minimize risks to the end user.

9. Summary of Non-Clinical Studies

All studies were performed using the Elecsys 2010 Immunoassay Analyzer.

9.1. Analytical Sensitivity

Studies were performed to determine the calibration formula and cutoff value for the Elecsys Anti-HBs Immunoassay. These studies were performed using several pre-production lots. The reference material evaluated was World Health Organization (WHO), Anti-Hepatitis B Immunglobulin, 1st Reference Preparation, 1977, Lot 26-1-77.

In a reference standardization, values are established that are traceable to the 1st IRP for anti-HBs (WHO) for six master calibrators covering the measuring range of the method (2 to 1000 IU/L). A lot specific master calibration curve is measured using lot-specific test kit reagents, Anti-HBs PreciControls and master calibrators (n=6). The shape of the lot specific master curve is characterized by a four parametric Rodbard function, which is stored in the lot specific reagent barcode. Lot specific calibrator values and lot specific Anti-HBs PreciControl target ranges are read from the lot specific master calibration curve and are encoded in the calibrator barcode card. The test design of the Elecsys Anti-HBs is that of a quantitative assay format with a cutoff threshold. The cutoff is set at the concentration of 10 IU/L, which is the internationally accepted threshold of protective immunity

The concentration at the cut-off of the Elecsys Anti-HBs Immunoassay was defined by using kit lots to assay a series of dilutions of known concentrations in IU/L of reference standards from WHO. With reference material from the WHO, the qualitative format of the Elecsys Anti-HBs Immunoassay identified the transition from reactive to non-reactive at 10 mIU/mL. An equivocal zone of +/-15% about this value is employed.

9.2. Seroconversion Panels

Six seroconversion panels from commercial vendors were analyzed by the Elecsys Anti-HBs Immunoassay and the reference anti-HBs assay applied in the qualitative format. The test results were generated at the site in Sacramento. The following table presents a summary of the Elecsys Anti-HBs Immunoassay test system results for the six panels in comparison to the reference method. Studies of commercially available seroconversion panels for HBV were performed at a clinical site. In these studies, compared to the reference assay result*, the first reactive time point for Elecsys occurred earlier in one panel, later in three panels and at the same time in a two panels.

*It is noteworthy that in these studies the reference assay used had a lower cutoff (2-5 mIU/mL range) than Elecsys (10-mIU/mL +/-15%).

Panel ID	Days to Anti-HBs Reactive Result from Initial Draw Date		Difference in Days to Anti-HBs Reactive Result (Reference – Elecsys)
	Reference Anti-HBs Assay	Elecsys Anti-HBs Assay	
01005	87	78	8
11004	186	>188	>-2
40565L	103	113	-10
51005	201	201	0
21469D	81	91	-10
22663D	140	140	0

9.3. Matrix Effects:

Studies were conducted to verify the types of blood collection tubes that can be used with the Elecsys Anti-HBs Immunoassay. In the first study, matched native specimens collected as serum and using different anticoagulants were studied. In the second study, 10 unspiked and 10 spiked with varying levels of anti-HBs were studied.

The studies support the use of EDTA plasma. Samples collected with EDTA plasma tubes show <10% bias when compared to serum.

9.4. Endogenous Interference

Samples with abnormally elevated levels of hemoglobin, lipids, bilirubin, total protein, heparin, and biotin were simulated using patient samples (negative and anti-HBs positive) spiked with the endogenous analyte of interest and compared to controls. The concentrations evaluated are summarized in the following table.

Endogenous Substance	Concentration Evaluated	Solvent	Reference Range
Hemoglobin	1600 mg/dl	Serum	0.5 - 5.0 mg/dl
Lipids	1500 mg/dl	Distilled/deionized water	10 - 190 mg/dl
Bilirubin	30 mg/dl	0.1 N NAOH	0.1 to 1.2 mg/dl
Total Protein	12 g/dl	Serum	6.0 - 7.8 g/dl
Heparin	10 U/ml	Serum	0.05 - 1.0 U/ml
Biotin	50 ng/ml	10 mM K ₂ PO ₄	0.06 - 0.43 ng/ml

The results of this study demonstrated that samples containing hemoglobin concentrations up to 1600 mg/dl, triglyceride levels up to 1500 mg/dl, bilirubin levels up to 30 mg/dl, total protein levels up to 12 g/dl, heparin levels up to 10 U/ml, or biotin levels up to 50 ng/ml may be tested accurately with the Elecsys Anti-HBs Immunoassay.

9.5. Carryover Study

Two studies using the Elecsys Anti-HBs Immunoassay were conducted to evaluate the effect of a sample highly reactive for anti-HBs on a following negative sample. Two patient samples highly reactive for anti-HBs were evaluated in this study. Sample 1, highly reactive for anti-HBs (1000 IU/L) was tested in three sample cups (H1, H2, H3) followed by replicates of an anti-HBs negative pool tested in five sample cups (L1, L2, L3, L4, L5). This sequence was repeated nine times in the same run for a total of ten high-low series. The study was repeated using a second Anti-HBs positive sample (6100 IU/L) into a low titer anti-HBs pool. The same testing sequence was performed as described for Sample 1. The L1 sample is the sample most susceptible to potential carryover from the high sample, L5 is the least susceptible. The difference between L1 and L5 for each high-low series was calculated and tested using the Wilcoxon signed rank test. The first study showed no statistically significant evidence of sample carryover. The second showed a slight elevation of the signal in L1. This signal, although statistically significant at 1.1 IU/L difference (p value: 0.002), was within total assay variability. The conclusion from these two studies is that clinically significant carryover did not occur on the Elecsys Anti-HBs Immunoassay when testing highly positive anti-HBs samples.

9.6. High Dose Hook Effect

Studies were run to assess the potential for a high dose hook effect (prozone effect). Samples with highly elevated levels of anti-HBs were diluted with anti-HBs negative serum. The diluted and undiluted samples were tested by the Elecsys Anti-HBs Immunoassay. Although a hook effect was observed for the Elecsys Anti-HBs Immunoassay, samples with anti-HBs concentrations up to 150,000 IU/L were detected as reactive by the Elecsys Anti-HBs Immunoassay and did not produce false negative test results.

9.7. Establishment of Cutoff

The cutoff for the Elecsys 2010 Anti-HBs Immunoassay was defined by using kit lots to assay a series of dilutions of known concentrations in IU/L of reference standards from WHO. With reference material from the WHO, the qualitative format of the Elecsys Anti-HBs Immunoassay identified the transition from reactive to non-reactive at 10 mIU/mL. An equivocal zone of +/-15% about this value is employed.

9.8. Stability Studies

To assess the real-time stability, whole kit samples were randomly selected from the individual lots of finished product. The kits and reagents were stored at the recommended storage temperature of 2-8°C, in temperature-controlled cabinets, for the duration of the ongoing stability studies. Temperatures in the storage cabinets were checked at regular intervals. The test measurement intervals started with the production date of the last kit reagent in the released kits, and continued at approximate 1, 3, 6, 9, 12, 15, 18, 24, and 30 month time intervals. Key stability parameters monitored for the Elecsys Anti-HBs Immunoassay were analytical sensitivity, results of internal control samples and the assay "Test Dynamic" (defined as quotient of the COI of Cal 2 over the COI of Cal 1).

Studies to characterize the stability of the Elecsys Anti-HBs Immunoassay and the Elecsys Anti-HBs PreciControl confirm a shelf life of 23 months for both when stored at 2-8 °C. Neither reagent should be stored frozen. If any reagent is inadvertently frozen prior to use it should be discarded.

The stability of kit reagents after temperature stress conditions was examined in several studies using different stress models. The results from the temperature stress studies indicated stability for all Elecsys Anti-HBs Immunoassay, Confirmatory Test, and PreciControl reagents for at least 1 week at 35°C. The recommended storage temperature for all the reagents is 2-8°C.

Additional opened reagent and on-board stability studies were conducted which demonstrated the following:

The Elecsys Anti-HBs Immunoassay and Elecsys Anti-HBs PreciControl kits may be used for 8 weeks once opened, when stored at 2-8°C

The Elecsys Anti-HBs Immunoassay reagent kit may be left on-board the Elecsys 2010 for 6 weeks.

One calibrator set may be used for a maximum of five calibration events and should be left on the Elecsys 2010 instrument only during calibration. The set may be left on the Elecsys 2010 instrument for up to 5 hours in total at 32°C.

One Anti-HBs PreciControl set should be left on the Elecsys 2010 instrument only when in use and may be used for a maximum of seven measurements. The Anti-HBs PreciControl set may be left on the instrument for up to seven hours in total at 32° C.

Calibrator should be stored at 2-8 ° C when not in use. Anti-HBs PreciControl may be used for seven quality control events at an ambient temperature of 32° C with each quality event lasting up to one hour and a maximum exposure to 32° C of up to seven hours. Controls should be stored at 2-8° C when not in use.

Calibrators may be used for five calibration events at an ambient temperature 32° C with each calibration event lasting up to one hour and a maximum exposure to 32° C of up to five hours.

Calibration stability studies confirmed that a single lot calibration may be used for one month with multiple reagent packs, as long as the same reagent lot is used. A calibration based on an individual reagent pack stored in the reagent compartment is stable for 7 days.

The results from the sample stability studies demonstrated that serum samples containing anti-HBs are stable for 6 days when stored at 2 – 8 °C and for three months when stored at -20°C. Plasma is stable for two days when stored at 2 – 8 °C and for three months when stored at -20°C. Samples may be frozen and thawed six times.

9.9. Analytical Specificity

Patient samples with various disease states were evaluated to determine the analytical specificity of the Elecsys Anti-HBs Immunoassay. Comparisons were made between the Elecsys Anti-HBs Immunoassay final results and the anti-HBs status using a FDA licensed anti-HBs test. All three sites participated in this evaluation; however the analysis has been made with the data from all sites combined with additional internal studies.

The table below summarizes the Elecsys Anti-HBs Immunoassay final test results compared to the HBV status for all sites combined.

Analytical Specificity Test Results: All Sites

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
Other Viral Hepatitis Infections	17	0	1	7	25
Other Infectious Diseases	53	0	0	20	73
Non-Viral Liver Diseases	20	0	0	4	24
Autoimmune Diseases	17	0	0	0	17
High Risk Populations	15	1	1	16	33
Post Influenza Vaccination	0	0	0	5	5
High Titer Immunoglobulins	35	0	0	2	37
Pregnancy	49	0	0	0	49
Total	206	1	2	54	263

The following sections present additional details to the table above by category.

Other Viral Hepatitis Infections: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs Immunoassay	Neg	Pos	Neg	Pos	Samples
Hepatitis A Infection	4	0	1	5	10
Hepatitis C Infection	6	0	0	2	8
Hepatitis E Infection	7	0	0	0	7
Total	17	0	1	7	25

For patients with other viral hepatitis infections, 96.0% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (24/25). One specimen from a patient with HAV infection was positive by Elecsys but was negative by the reference assay.

Other Infectious Diseases: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
Cytomegalovirus	10	0	0	0	10
Epstein-Barr Virus	6	0	0	4	10
Herpes Simplex Virus	11	0	0	5	16
Rubella Virus	16	0	0	0	16
Human Immunodeficiency Virus	5	0	0	5	10
Syphilis	3	0	0	6	9
Toxoplasmosis	2	0	0	0	2
Total	53	0	0	20	73

For patients with other infectious diseases, 100% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (73/73).

Non-Viral Liver Disease: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
Non-Viral Liver Disease	17	0	0	3	20
Alcoholic Hepatitis	3	0	0	1	4
Total	20	0	0	4	24

For patients with non-viral liver diseases, including alcoholic hepatitis, 100% agreement was observed between Elecsys Anti-HBs Immunoassay final results and reference anti-HBs test results (24/24).

Autoimmune Diseases: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
Rheumatoid Factor	17	0	0	0	17
Total	17	0	0	0	17

For patients with rheumatoid factor, 100% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (17/17).

High Risk Populations: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs Immunoassay	Neg	Pos	Neg	Pos	Samples
Transplant Recipients	6	0	0	7	13
Chronic Dialysis	5	1	0	4	10
Intravenous Drug Users	4	0	1	5	10
Total	15	1	1	16	33

For patients at high risk of acquiring HBV infection, 93.9% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (31/33). One specimen from a patient undergoing chronic dialysis was positive by the reference assay but negative on initial testing with Elecsys. The specimen was not positive for any other HBV marker. On re-test, the specimen was positive in one test and equivocal on the second by Elecsys. One other specimen from an IV drug user was positive by Elecsys but negative by the reference test. This patient was serologically classifiable as recovered from past HBV infection, having antibodies to HBc.

Post Influenza Vaccination: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
Post Influenza Vaccination	0	0	0	5	5

For patients having recently received a vaccination for influenza, 100% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (5/5). All five subjects presented serology consistent with having been vaccinated against HBV.

High Titer Immunoglobulins: Elecsys Final Results

Elecsys® Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
High Titer IgG	18	0	0	0	18
High Titer IgA	15	0	0	2	17
High Titer IgM	2	0	0	0	2
Total	35	0	0	2	37

For patients with high titer immunoglobulins, 100% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (37/37).

Pregnancy: Elecsys Final Results

Elecsys [®] Anti-HBs Immunoassay	Neg	Neg	Pos	Pos	Total
Reference anti-HBs immunoassay	Neg	Pos	Neg	Pos	Samples
Pregnancy	49	0	0	0	49

For patients who were pregnant, 100% agreement was observed between Elecsys Anti-HBs Immunoassay final results and the reference anti-HBs test results (49/49).

9.10. Reproducibility (Precision)

In a multi-center precision study with a design based on principles contained in the NCCLS draft guideline EP5-T2¹, results from a series of negative and positive samples run on the Elecsys 2010 analyzer at three centers over 20 days demonstrated a within run precision ranging from 1.8 to 7.7% CV. Between day precision, which also included within run and between run components, ranged from 2.9 to 14.7% CV; total precision, which included all precision components, ranged from 7.5 to 21.4 CV.

Reproducibility Study Results for the Elecsys Anti-HBs Immunoassay

Panel Member	Mean	Within Run		Between Day *		Between Lot		Between Site		Total **	
	(mIU/mL)	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
1	5.88	0.45	7.7	0.86	14.7	0.26	4.4	0.66	11.2	1.26	21.4
2	21.99	0.75	3.4	1.21	5.5	0.63	2.9	0.50	2.3	1.74	7.9
3	42.27	0.95	2.3	3.54	4.1	1.99	4.7	1.61	3.8	3.35	7.9
4	87.45	1.64	1.9	2.56	2.9	4.42	5.1	2.96	3.4	6.69	7.7
5	154.3	3.44	2.2	5.98	3.9	7.64	5.0	5.16	3.3	11.64	7.6
6	447.3	7.90	1.8	16.35	3.7	23.74	5.3	14.46	3.2	33.53	7.5

* Includes between run and between day components.

** Includes within run, between run, between day, between site/ lot interaction, between lot and between site components.

10. Summary of Clinical Studies

10.1. Expected Results

Of 1350 prospective subjects participating in the Elecsys anti-HBs clinical study, 44.4% (n = 600) were first time blood donors, asymptomatic for viral hepatitis. All of these 600 subjects were enrolled in Sacramento, CA. The group was Caucasian (61%), African American (10%), Hispanic (2%), Asian (1%) with 26% electing not to provide

¹ National Committee for Clinical Laboratory Standards. Evaluation of Precision Performance of Clinical Chemistry Devices - Second Edition; Tentative Guideline. NCCLS document EP5-T2. NCCLS, 771 East Lancaster Avenue, Villanova, Pennsylvania 19085, 1992.

this information. The group was 58% male and 42% female ranging in age from 17 to 73 years.

The table below summarizes the Elecsys Anti-HBs negative and confirmed positive results by age range and gender.

		Elecsys Anti-HBs Immunoassay			
Age	Gender	Pos	Equiv	Neg	Total
< 10	Male	0	0	0	0
	Female	0	0	0	0
10 – 19	Male	21	1	155	177
	Female	19	1	95	115
20 – 29	Male	11	0	60	71
	Female	6	0	36	42
30 – 39	Male	7	0	38	45
	Female	7	0	39	46
40 – 49	Male	5	0	30	35
	Female	9	0	23	32
50 – 59	Male	1	0	15	16
	Female	2	0	11	13
60 – 69	Male	0	0	2	2
	Female	1	0	3	4
70 – 79	Male	0	0	1	1
	Female	0	0	1	1
80 – 89	Male	0	0	0	0
	Female	0	0	0	0
90 – 99	Male	0	0	0	0
	Female	0	0	0	0
Unknown	Male	0	0	0	0
	Female	0	0	0	0
Totals	Male	45	1	301	347
	Female	44	1	208	253
	All	89	2	509	600

The 750 remaining subjects were enrolled from populations considered at risk for viral hepatitis due to lifestyle or behavior. Of these, 449 were outpatients of a health screening clinic and 301 were hospitalized patients. Of the hospitalized and health screening clinic patients, 446 of the subjects were enrolled in Memphis, TN, and 304 in Miami, FL. This collective group was African American (26%), Caucasian (19%), Hispanic (5%), Asian (<1%) or other (<1%) with 50% electing not to provide this information. The group was 49% male and 51% female ranging in age from 8 to 94 years.

The table below summarizes the distribution of Elecsys Anti-HBs Immunoassay results by age range and gender.

		Elecsys Anti-HBs Immunoassay			
Age	Gender	Pos	Equiv	Neg	Total
< 10	Male	0	0	1	1
	Female	0	0	0	0
10 – 19	Male	0	0	4	4
	Female	0	0	7	7
20 – 29	Male	58	0	48	106
	Female	42	0	32	74
30 – 39	Male	7	0	46	53
	Female	11	0	45	56
40 – 49	Male	8	0	48	56
	Female	13	0	53	66
50 – 59	Male	9	0	44	53
	Female	5	0	39	44
60 – 69	Male	1	1	36	38
	Female	8	1	46	55
70 – 79	Male	3	0	30	33
	Female	7	0	40	47
80 – 89	Male	4	0	8	12
	Female	4	0	15	19
90 – 99	Male	0	0	1	1
	Female	1	0	2	3
Unknown	Male	7	1	6	14
	Female	1	0	7	8
Totals	Not Given	0	0	0	0
	Male	97	2	272	371
	Female	92	1	286	379
	All	189	3	558	750

10.2. Clinical Performance

A multi-center prospective study was conducted to characterize the performance of the Elecsys Anti-HBs Immunoassay with individuals from defined populations. All subjects were tested using FDA-approved/cleared reference methods in strict accordance with the manufacturer's package insert instructions. The collection sites for the specimens were located in Sacramento, CA (44.5%), Memphis, TN (33.0%), and Miami, FL (22.3%).

Of the 1350 prospective subjects participating in the anti-HBs clinical study, 44.4% (n=600) were first time blood donors, asymptomatic for viral hepatitis and 750 subjects were at risk of HBV infection due to lifestyle or behavior. Of the 750 at risk subjects, 59.9% (n=449) were outpatients of a health screening clinic and 40.1% (n=301) were hospitalized patients.

The first time blood donors were Caucasian (61%), African American (10%), Hispanic (2%), and Asian (1%) with 26% electing not to provide this information. The group was 58% male and 42% female ranging in age from 17 to 73 years. The at risk subjects were African American (21%), Caucasian (19%), Hispanic (5%), Asian (<1%) or other (<1%) with 55% electing not to provide this information. This group was 49% male and 51% female ranging in age from 8 to 94 years.

The performance of the Elecsys Anti-HBs Immunoassay was analyzed relative to the reference anti-HBs reported results for all 1350 specimens. Complete testing using FDA approved methods for all six HBV markers including HBsAg, HBeAg, anti-HBc, anti-HBc IgM, anti-HBe and anti-HBs, thus allowing single point serological classifications of HBV status, was available for 348 of the subjects.

HBV Classification	HBsAg	HBeAg	anti-HBc IgM	anti-HBc (total)	anti-HBe	anti-HBs
Acute	Pos	+ or -	-	-	-	-
Acute	Pos	+ or -	pos	pos	+ or -	-
Chronic*	pos > 6 mo.					
Chronic	Pos	+ or -	-	pos	+ or -	+ or -
Early Recovery	-	-	pos	pos	+ or -	+ or -
Recovery	-	-	-	pos	pos	+ or -
Recovered	-	-	-	pos	-	+ or -
Vaccinated	-	-	-	-	-	pos
Not Previously Infected	-	-	-	-	-	-
Uninterpretable	Pos	-	pos	pos	pos	pos
Uninterpretable	-	pos	-	-	-	-
Uninterpretable	-	pos	-	-	-	pos
Uninterpretable	-	pos	-	pos	-	pos
Uninterpretable	-	-	-	-	pos	pos
Uninterpretable	-	-	-	-	-	equiv

- Subjects known, by testing, to have HBsAg persisting for greater than 6 months.

Results by Specimen Classification

The following table compares the Elecsys anti-HBs results with the reference results for the prospective studies with first time blood donors by HBV classification.

HBV Classification	Anti-HBs Result Reference EIA						Total
	-			+			
	Elecys Anti-HBs Result			Elecys Anti-HBs Result			
	-	+	I*	-	+	I*	
Acute	0	0	0	0	0	0	0
Chronic	0	0	0	0	0	0	0
Early Recovery	0	0	0	0	1	0	1
Recovery	0	0	0	0	2	0	2
Recovered	0	0	0	0	1	0	1
Uninterpretable	0	0	0	0	0	0	0
HBV Vaccine Response	0	0	0	1	85	1	87
Not Previously Infected	30	0	1	0	0	0	31
Not Classified	476	0	0	1	0	0	477
Total	506	0	1	2	89	1	599

HBV Classification	Anti-HBs Result Reference EIA			Total
	Indeterminate (equivocal)			
	Elecys Anti-HBs Result			
	-	+	I*	
Acute	0	0	0	0
Chronic	0	0	0	0
Early Recovery	0	0	0	0
Recovery	0	0	0	0
Recovered	0	0	0	0
Uninterpretable	0	0	0	0
HBV Vaccine Response	0	0	0	0
Not Previously Infected	0	0	0	0
Not Classified	1	0	0	1
Total	1	0	0	1

The table below compares the Elecys anti-HBs results with the reference results for the prospective studies with subjects at risk for HBV infection due to lifestyle or behavior by HBV classification.

HBV Classification	Anti-HBs Result Reference EIA						Total
	-			+			
	Elecys Anti-HBs Result			Elecys Anti-HBs Result			
	-	+	I*	-	+	I*	
Acute	1	0	0	0	0	0	1
Chronic	1	0	0	0	0	0	1
Early Recovery	0	0	0	0	0	0	0
Recovery	0	0	0	1	23	0	24
Recovered	2	2	1	3	20	0	28
Uninterpretable	0	0	0	0	2	0	2
HBV Vaccine Response	0	0	0	11	122	1	134
Not Previously Infected	30	3	0	0	0	0	33
Not Classified	505	2	0	2	14	1	524
Total	539	7	1	17	181	2	747

HBV Classification	Anti-HBs Result Reference EIA			Total
	Indeterminate (equivocal)			
	Elecys Anti-HBs Result			
	-	+	I*	
Acute	0	0	0	0
Chronic	0	0	0	0
Early Recovery	0	0	0	0
Recovery	0	0	0	0
Recovered	0	0	0	0
Uninterpretable	2	1	0	3
HBV Vaccine Response	0	0	0	0
Not Previously Infected	0	0	0	0
Not Classified	0	0	0	0
Total	2	1	0	3

Percent Agreement

The table below summarizes the percent agreement between the Elecys Anti-HBs Immunoassay and the anti-HBs reference assay with first time blood donors by specimen classification exclusive of the two specimens with equivocal results by the reference assay. The table also provides the upper and lower 95% Exact Confidence Intervals.

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	NA	NA	NA	NA
Chronic	NA	NA	NA	NA
Early Recovery	100 (1/1)	2.5 – 100.0	NA	NA
Recovery	100 (2/2)	15.9 – 100.0	NA	NA
Recovered	100 (1/1)	2.5 – 100.0	NA	NA
Uninterpretable	NA	NA	NA	NA
HBV Vaccine Response	97.7 (85/87)	91.9 – 99.7	NA	NA
Not Previously Infected	NA	NA	96.8 (30/31)	83.3 – 99.9
Not classified	0 (0/1)	NA	100 (476/476)	99.2 – 100.0
	96.7 (89/92)	90.8 – 99.3	99.8 (506/507)	98.9 – 100.0

The table below summarizes the percent agreement between the Elecsys Anti-HBs Immunoassay and the anti-HBs reference assay with subjects at risk for HBV infection due to lifestyle or behavior by specimen classification exclusive of the seven specimens with equivocal results by the reference assay. The table also provides the upper and lower 95% Exact Confidence Intervals.

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	NA	NA	100 (1/1)	2.5 – 100.0
Chronic	NA	NA	100 (1/1)	2.5 – 100.0
Early Recovery	NA	NA	NA	NA
Recovery	95.8 (23/24)	78.9 – 99.9	NA	NA
Recovered	87.0 (20/23)	66.4 – 97.2	40.0 (2/5)	5.3 – 85.3
Uninterpretable	100 (2/2)	15.9 – 100.0	NA	NA
HBV Vaccine Response	91.0 (122/134)	84.9 – 95.3	NA	NA
Not Previously Infected	NA	NA	90.9 (30/33)	75.7 – 98.1
Not classified	82.4 (14/17)	56.6 – 96.2	99.6 (505/507)	98.6 – 100.0
	90.5 (181/200)	85.6 – 94.2	98.5 (539/547)	97.1 – 99.4

Percent Agreement of the Elecsys Anti-HBs Immunoassay for Subjects at Various Discrete Stages of HBV Infection or Recovery

The performance of the Elecsys Anti-HBs Immunoassay was studied with archived specimens representing various discrete stages of HBV infection or recovery. The table below compares the Elecsys Anti-HBs Immunoassay with the anti-HBs reference assay results by specimen classification.

HBV Classification	Anti-HBs Result Reference EIA						Total
	Elecsys Anti-HBs Result			Elecsys Anti-HBs Result			
	-	+	I*	-	+	I*	
Acute	152	0	1	0	0	0	153
Chronic	177	2	0	5	9	1	194
Early Recovery	1	0	0	0	3	0	4
Recovery	0	0	1	0	35	0	36
Recovered	4	0	0	1	17	0	22
Uninterpretable	3	0	0	1	1	0	5
HBV Vaccine Response	0	0	0	0	6	0	6
Not Previously Infected	10	0	0	0	0	0	10
Not Classified	1	0	0	0	0	0	1
Total	348	2	2	7	71	1	431

HBV Classification	Anti-HBs Result Reference EIA			Total
	Indeterminate (equivocal)			
	Elecys Anti-HBs Result			
	-	+	I*	
Acute	0	0	0	0
Chronic	2	0	0	2
Early Recovery	0	0	0	0
Recovery	0	0	0	0
Recovered	0	0	0	0
Uninterpretable	0	0	0	0
HBV Vaccine Response	0	0	0	0
Not Previously Infected	0	0	0	0
Not Classified	0	0	0	0
Total	2	0	0	2

Percent Agreement

The table below summarizes the percent agreement between the Elecys Anti-HBs Immunoassay and the anti-HBs reference assay by specimen classification exclusive of the five specimens with equivocal results by the reference assay. The table also provides the upper and lower 95% Exact Confidence Intervals.

HBV Classification	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Acute	NA	NA	99.4 (152/153)	96.4 – 100.0
Chronic	60.0 (9/15)	34.9 – 90.1	98.9 (177/179)	96.0 – 99.9
Early Recovery	100 (3/3)	29.5 – 100.0	100.0 (1/1)	2.5 – 100.0
Recovery	100 (35/35)	90.0 – 100.0	0 (0/1)	0.0 – 97.5
Recovered	94.4 (17/18)	72.7 – 99.9	100.0 (4/4)	40.0 – 100.0
Uninterpretable	50.0 (1/2)	1.3 – 98.7	100 (3/3)	29.5 – 100.0
HBV Vaccine Response	100 (6/6)	54.3 – 100.0	NA	NA
Not Previously Infected	NA	NA	100 (10/10)	69.3 – 100.0
Not classified	NA	NA	100 (1/1)	2.5 – 100.0
Overall	89.9 (71/79)	83.6 – 97.1	98.9 (348/352)	97.1 – 99.7

Clinical Performance with Individuals Having Received Hepatitis B Vaccine

A retrospective study was conducted to evaluate specimens from 55 subjects who had received a full series of at least three HBV vaccinations. Each sample was studied using the Elecys Anti-HBs Immunoassay and the qualitative methodology of the reference anti-HBs EIA. At the time of final testing, the specimen was required to be

free of all HBV markers (except anti-HBs) to substantiate that the reactivity was a consequence of vaccination and not natural infection.

The following table presents the results of the Elecsys Anti-HBs Immunoassay results compared to the reference anti-HBs EIA test results. The agreement between the Elecsys and the reference assay was 98.2%, with 54 concordant positives and one specimen positive by the reference assay but equivocal by Elecsys.

		Reference anti-HBs Immunoassay		
		Pos	Equivocal	Neg
Elecsys Anti-HBs Immunoassay	Pos	54	0	0
	Equivocal	1	0	0
	Neg	0	0	0

	% (N)	95% Exact Confidence Interval
Positive Percent Agreement with the Reference Method	98.2 (54/55)	90.3 – 100.0
Negative Percent Agreement with the Reference Method	NA	NA

Clinical Performance with Matched Pre- and Post-Vaccination Samples

The performance of the Elecsys Anti-HBs Immunoassay was assessed in subjects undergoing vaccination to HBV. Paired samples from 40 subjects purported never to have been vaccinated or previously exposed to HBV were evaluated at the University of Miami site. The inclusion criteria required no history of HBV vaccination in the pre-vaccination specimen and negative serology for HBV markers in both the pre- and post-vaccination specimens. The following table presents the results of the final Elecsys anti-HBs test results compared to the reference anti-HBs EIA test results. The agreement between Elecsys and the reference assay was 100%, with 38 concordant positives and 42 concordant negatives.

Pre-Vaccination Panel

Reference anti-HBs Immunoassay

		Pos	Equivocal	Neg
Elecsys Anti-HBs Immunoassay	Pos	0	0	0
	Equivocal	0	0	0
	Neg	0	0	40

Post-Vaccination Panel

Reference anti-HBs Immunoassay

		Pos	Equivocal	Neg
Elecsys Anti-HBs Immunoassay	Pos	38	0	0
	Equivocal	0	0	0
	Neg	0	0	2

Reference anti-HBs Immunoassay

		Pos	Equivocal	Neg
Elecsys Anti-HBs Immunoassay	Pos	38	0	0
	Equivocal	0	0	0
	Neg	0	0	42

	% (N)	95% Exact Confidence Interval
Positive Percent Agreement with the Reference Method	100.0 (38/38)	90.8 – 100.0
Negative Percent Agreement with the Reference Method	100.0 (42/42)	91.6 – 100.0

11. Conclusions Drawn from PMA Studies

In multi-centered clinical trials in the United States, the Elecsys Anti-HBs Immunoassay was shown to exhibit clinical sensitivity and specificity that correlate well to other commercially available similar licensed devices.

The clinical evaluations provide valid scientific evidence of the clinical and diagnostic use of the automated Elecsys Anti-HBs Immunoassay for the qualitative determination of anti-HBs in human serum and plasma (EDTA). The results from these studies also support the clinical and diagnostic performance of the Elecsys anti-HBs PreciControl reagents.

The PMA studies provide reasonable assurance that the Elecsys Anti-HBs Immunoassay safely and effectively be used to determine the patient's susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown. These studies establish the use of this assay with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection and for serological evidence of seroconversion from hepatitis B virus (HBV) infection.

12. Safety and Benefit/Risk Analysis

As a diagnostic test, the anti-HBs assay 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 removed. The benefits to HBV-infected individuals tested by these devices outweigh any potential adverse event or risk to the patient or user due to device malfunction or operator error.

The potential risks seen for *in vitro* diagnostic tests are not unusual in the laboratory setting, and appropriate warnings for these risks are contained in the labeling and package insert instructions for these devices. Standard good laboratory practices are considered sufficient to minimize the risks to the end user.

13. Panel Recommendation

Pursuant to Section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Microbiology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.

14. CDRH Decision on application:

FDA issued an approval order on February 28, 2002.

The applicant's manufacturing facility was inspected on July 20, 2000 and found to be in compliance with the devices Good Manufacturing Practice regulation.

15. Approval Specifications:

Directions for Use: See labeling

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

Postapproval Requirements and Restrictions: See approval order.