

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Antibodies to Hepatitis C Antigen Assay
Antibodies to Hepatitis C Antigen Control

Device Trade Name: Elecsys® Anti-HCV Immunoassay and
Elecsys® PreciControl Anti-HCV on the cobas e 601
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: P090008

Date of FDA Notice of Approval: April 29, 2010

Expedited: *not applicable*

II. INDICATIONS FOR USE

Elecsys® Anti-HCV Immunoassay

The Elecsys Anti-HCV assay is an in vitro diagnostic test for the qualitative detection of total antibodies to hepatitis C virus (anti-HCV) in human serum or plasma (potassium EDTA, lithium heparin and sodium heparin). Assay results, in conjunction with other laboratory results and clinical information, may be used to aid in the presumptive diagnosis of HCV infection in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis C infection. The test does not determine the state of infection or associated disease. The electrochemiluminescence immunoassay "ECLIA" is intended for use on the cobas e 601 Immunoassay Analyzer.

Elecsys® PreciControl Anti-HCV

Elecsys PreciControl Anti-HCV is used for quality control of the Elecsys Anti-HCV immunoassay on the cobas e 601 Immunoassay Analyzer.

III. CONTRAINDICATIONS

- Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted by or on the order of a physician.

Summary of Safety and Effectiveness Data

- Assay performance characteristics have not been established in patients under the age of 21, pregnant women, or in populations of immunocompromised or immunosuppressed patients.
- This assay has not been FDA licensed for the screening of blood, plasma and tissue donors

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Elecsys® Anti-HCV Immunoassay on the cobas e 601 Immunoassay Analyzer labeling.

V. DEVICE DESCRIPTION

Kit Configuration and Component

The key components of the Elecsys® Anti-HCV Immunoassay on the cobas e 601 Immunoassay Analyzer reagent kit are as follows:

- The M reagent consists of Streptavidin coated microparticles ("beads") in buffer with preservatives. The reagent is provided ready-to-use and should be stored at 2-8°C.
- The R1 reagent consists of a buffer with a reducing agent, EDTA and preservative. The reagent is used for the preparation of the working solution in R1.
- The R2 reagent consists of a buffer with a reducing agent, EDTA and preservative. The reagent is used for the preparation of the working solution in R2.
- The R1a reagent consists of the lyophilized biotinylated HCV specific antigens (recombinant antigen NS3 region, peptide core region, and peptide NS4 region), in a buffered bovine plasma protein solution.
- The R2a reagent consists of the lyophilized ruthenylated HCV specific antigens (recombinant antigen NS3 region, peptide core region, and peptide NS4 region), in a buffered bovine plasma protein solution.
- The R1b reagent consists of water with preservative.
- The R2b reagent consists of water with preservative.
- The Cal1 reagent consists of a buffered human serum matrix, negative for anti-HCV.
- The Cal2 reagent consists of a buffered human serum matrix, low positive for anti-HCV antibodies.

Summary of Safety and Effectiveness Data

2. The Elecsys® PreciControl Anti-HCV contains two reagents:

- PreciControl 1, PC A-HCV1
8 bottles, each containing 1.3 mL of human serum negative for anti-HCV, with a preservative.
- PreciControl 2, PC A-HCV2
8 bottles, each containing 1.3 mL of human serum positive for anti-HCV, with a preservative.

Assay Principle and Format

The Elecsys® Anti-HCV Immunoassay is an immunoassay based on a sandwich principle. The assay detects total antibodies to HCV virus in serum and plasma samples; the total duration of the assay is 18 minutes. The principle of the device methodology is as follows:

- 1st incubation: 40 µL of sample, 60 µL of a reagent containing biotinylated HCV antigens and 60 µL of a reagent containing HCV antigens labeled with a ruthenium complex (Tris (2,2' -bipyridyl)ruthenium(II)complex (Ru(bpy)₃²⁺) react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via 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 cobas e 601 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-HCV calibration.

The Elecsys® PreciControl Anti-HCV

The Elecsys PreciControl Anti-HCV contains total Anti-HCV antibodies in human serum in negative and positive concentration ranges. The controls are used for monitoring the performance of Elecsys Anti-HCV immunoassay.

Calibration and Interpretation of Results

The Elecsys® Anti-HCV Immunoassay is calibrated by using the Calibrator 1 and Calibrator 2 which are provided with the reagent kit. The presence or absence of anti-HCV in the sample is determined by comparing the electrochemiluminescent signal in the reaction to the cutoff signal determined from an active Elecsys Anti-HCV calibration curve. If the electrochemiluminescent

Summary of Safety and Effectiveness Data

signal of the sample is greater than or equal to the cutoff signal, the sample is considered reactive for anti-HCV.

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-HCV. The result of a sample is given in the form of a cutoff-index COI (signal sample/signal cutoff) along with a result interpretation as follows:

- “non-reactive” (COI < 0.90)
- “border” (= borderline) (0.90 ≤ COI < 1.00)
- “reactive” (COI ≥ 1.00)

The following tables summarize the recommended testing algorithms that are then performed and recommended to reconcile the initial test results:

Initial Elecsys Anti-HCV Assay			
COI	Result	Interpretation of results	Retest Procedure
< 0.90	non-reactive*	No antibodies to HCV were detected	No Retest required
0.90 ≤ COI < 1.00	Border	Border line zone (undetermined)	Retest in duplicate with the Elecsys Anti-HCV assay.
COI ≥ 1.00	reactive	Antibodies to HCV detected	Presumptive HCV infection, follow CDC recommendations for supplemental testing.

Summary of Safety and Effectiveness Data

Final Elecsys Anti-HCV Assay			
Initial Result	Result after retest (COI)	Final results	Interpretation of results
non-reactive	No Retest required	NON-REACTIVE*	Antibodies to HCV were not detected; does not exclude the possibility of exposure to HCV
Border	If 2 of the 3 results have a COI < 1.00	NON-REACTIVE	Antibodies to HCV were not detected; does not exclude the possibility of exposure to HCV
	If 2 of the 3 results have a COI ≥ 1.00	REACTIVE	Presumptive evidence of antibodies to HCV. Follow CDC recommendations for supplemental testing.
reactive	No Retest required	REACTIVE	Presumptive evidence of antibodies to HCV. Follow CDC recommendations for supplemental testing

*Please note: If a patient is known to be at high risk of HCV infection, or is symptomatic, and the physician's suspicion of HCV infection is high, HCV RNA testing is often employed and is of diagnostic value, even after an initial negative anti-HCV test result.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

VII. MARKETING HISTORY

The Elecsys® Anti-HCV Immunoassay and PreciControl is currently marketed in Europe, Asia and in South America. The device has not been withdrawn to date from the market in any country for reasons relating to the safety and effectiveness of the device. The following table provides the list of countries where the product is distributed:

Argentina	Hungary	Poland
Australia	India	Romania
Austria	Indonesia	Russian Federation
Belgium	Italy	Singapore
Brazil	Japan	Slovakia
Canada	Kenya	South Africa
Chile	Korea	Spain
China	Latvia	Sweden
Colombia	Malaysia	Switzerland
Czech Republic	Mexico	Taiwan
Ecuador	Netherlands	Thailand
Finland	New Zealand	Turkey
France	Pakistan	Uganda
Germany	Panama	United Kingdom
Greece	Peru	Venezuela
Hong Kong	Philippines	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

When used according to the instructions in the package insert, there are no direct adverse effects of this device on the health of the user. 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.

A false nonreactive (false negative) anti-HCV result in a diagnostic setting may lead to a patient with HCV going unidentified. Under these circumstances, there is a safety concern for both the patient and the public, since such individuals may be capable of transmitting HCV infection. However, if a patient is known to be at high risk of HCV infection, or is symptomatic, and the physician's suspicion of HCV infection is high, HCV RNA testing is often employed and is of diagnostic value, even after an initial negative anti-HCV test result.

A false reactive (false positive) result using an anti-HCV assay is not considered a patient or public health concern because a reactive enzyme immunoassay (EIA) result in a clinical laboratory should be followed up with supplemental tests (e.g., strip immunoblot assay (SIA) and/or polymerase chain reaction (PCR) for detection of HCV RNA) to determine inactive or resolved infection versus active HCV replication.¹ Treatment of the patient with chronic HCV infection is initiated only after extensive clinical, laboratory and behavioral assessment of the patient (e.g., elevated ALT levels for six months,

Summary of Safety and Effectiveness Data

detectable serum HCV RNA, liver biopsy with portal fibrosis, and abstinence from drugs and alcohol).

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.

IX. SUMMARY OF PRECLINICAL STUDIES

All non-clinical studies were performed at Roche Diagnostics Laboratories using the Elecsys® Anti-HCV immunoassay and the Elecsys® PreciControl Anti-HCV on the cobas e 601 immunoassay analyzer. The studies are described below.

Cutoff Determination

The cut-off value was established with in-house studies by measuring a panel of 682 samples, including seroconversion panels, samples from dialysis patients, pregnant women, potentially cross-reactive samples, anti-HCV positive samples, blood donor samples from the Bavarian Red Cross, and samples from a commercial performance panel including different genotypes.

A Receiver Operator Curve (ROC) analysis was used to optimize sensitivity and specificity. For verification, in-house studies were performed using 505 samples with cohorts including seroconversion panels, Anti-HCV positive samples, and blood donor samples from the Bavarian Red Cross. Validation of the cut off was performed by external clinical studies.

Endogenous Interferences:

To evaluate the effect of elevated levels of hemoglobin, bilirubin, intralipid, biotin, and total protein on the Elecsys Anti-HCV assay, one negative, one high negative, one low positive, and one positive Anti-HCV sample were spiked with each of the potential interferents. Each interferent was evaluated at 10 concentrations. All samples were tested in duplicate. The acceptance criteria for samples < 1.0 s/co was a recovery s/co within +/- 0.2 s/co when compared to the initial unspiked result. The acceptance criteria for samples >= 1.0 s/co was a recovery of 80 – 120% s/co when compared to the initial unspiked result. The average percent recovery of spiked versus unspiked treatments ranged from 86 – 113%.

Study results:

Interferent tested	No interference up to
Bilirubin	50 mg/dL
Intralipid	2100 mg/dL
Biotin	50 ng/mL
Total Protein	12.0 g/dL

Summary of Safety and Effectiveness Data

The data from this study demonstrated that samples containing hemoglobin at concentrations ≥ 0.1 g/dL result in reduced recovery of anti-HCV. Samples that show visible signs of hemolysis should not be analyzed with the Elecsys Anti-HCV assay.

Drug Interferences

A drug interference study was performed on the cobas e 601 immunoassay analyzer with 18 common therapeutic drugs and two special therapeutic drugs used as antiviral therapeutics in chronic hepatitis C treatments (alpha-interferon and ribavirin). Each drug was spiked into a negative, low positive and positive sample; each sample was analyzed in triplicate. Each drug was found to be non-interfering. Since these studies were performed *in vitro*, they do not assess the potential interference when the drugs are metabolized *in vivo*.

Compound	Concentration
Acetyl cysteine	150 mg/L
Ampicillin-Na	1000 mg/L
Ascorbic acid	300 mg/L
Ca- Dobesilate	200 mg/L
Cyclosporine	5 mg/L
Cefoxitin	2500 mg/L
Heparin	5000 U
Intralipid	10,000 mg/L
Levodopa	20 mg/L
Methyldopa+ 1.5	20 mg/L
Metronidazole	200 mg/L
Phenylbutazone	400 mg/L
Tetracycline	50 mg/L
Acetylsalicylic acid	1000 mg/L
Rifampicin	60 mg/L
Acetaminophen	200 mg/L
Ibuprofen	500 mg/L
Theophylline	100 mg/L
Alpha-interferon	3000 U mg/L
Ribavirin	1200 mg/L

Matrix Effects:

Studies were conducted to evaluate the suitability of five types of blood collection tubes to be used with the Elecsys Anti-HCV assay. Samples were collected into matched serum and plasma collection tubes from 40 donors and assayed in triplicate. Forty matched pairs were collected in the evaluation of each: serum/gel separation tubes, lithium heparin plasma, K₂-EDTA plasma, sodium heparin plasma, and sodium citrate plasma. The study was conducted using negative, high-negative, low-positive, and positive samples for Anti-HCV. On average the serum/gel separation tubes, lithium heparin plasma, K₂-EDTA plasma, and sodium heparin plasma tube types were within $\pm 20\%$ difference when compared to the control tube type (plastic serum).

The studies support the use of serum/gel separation tubes and plasma collected using blood collection tubes containing the following anticoagulants: Lithium heparin plasma, K₂ EDTA plasma and sodium heparin plasma. However, the data showed a significant overall negative bias when using sodium citrate plasma tubes. The use of sodium citrate plasma tubes is not

Summary of Safety and Effectiveness Data

a recommended specimen matrix for this test. The appropriate limitation appears in the package insert.

Carryover Study

On the cobas e 601 analyzer, the use of disposable tips for sample pipetting and for reagent pipetting excludes any risk of carry over by design of test system. A study was performed to determine the extent of signal carry over for the Elecsys Anti-HCV immunoassay in the measuring cell. Seven Anti-HCV negative samples were tested in triplicate. Then seven different Toxo-IgG samples which create high signals (≥ 2 Mio counts) in Elecsys Toxo-IgG were tested followed again by the respective Anti-HCV negative samples tested with Elecsys Anti-HCV in triplicate. The deviation of the first signal value of the negative sample after the high-signal-generating sample was compared to the medium signal of the triplicate measurements before testing the high-signal generating sample. The signal carryover effect varied from 5-13%.

High Dose Hook Effect

A study was performed to verify that a high dose hook effect does not lead to false negative results. Three high titer positive samples were diluted in human HCV negative serum in at least 11 dilution steps to generate a dilution series that covers the range from negative to high positive s/co values. Samples were measured in three fold determination. The study demonstrated that at very high Anti-HCV antibody concentrations, a high dose hook effect is observed. However, even extremely high Anti-HCV antibody concentrations are recognized correctly as highly positive by the Anti-HCV assay. No false negative results due to high dose hook effects have been observed.

Serum Sample Stability:

Four studies were performed to verify the stability of patient serum samples using the Elecsys Anti-HCV Immunoassay. The potential influence of storage of samples for 21 days at 2-8°C, 4 days at 25°C, -20°C for 3 months, and 6 freeze/thaw cycles was evaluated with 12 Anti-HCV serum samples (negative, high negative, low positive, positive) measured in triplicate determination. Time points tested were day 0 (unstressed), 2 days, 7 days, 14 days, and 21 days for the 21 days at 2-8°C testing. Time points tested for 4 days at 25°C were day 0 (unstressed), day 1, day 2, day 3 and day 4. Time points tested for -20°C at 3 months was time 0 (unstressed) and 3 months. Time points tested for the 6 freeze/thaw cycles was time 0 (unstressed) and after each freeze/thaw cycle. Recovery after storage for each test was calculated based on sample to cut-off index. The results demonstrated that serum specimens may be stored for 21 days at 2-8 °C, for 3 months at -20 °C, 4 days at 25°C, and may be subjected to 6 freeze-thaw cycles prior to testing by the Elecsys Anti-HCV Immunoassay.

Elecsys Anti-HCV Reagent Stability:

To assess the real-time stability, whole kit samples from three lots were randomly selected from the individual lots of finished product. 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. Temperatures in the storage area were checked at predetermined intervals. The test measurement intervals started with the production date of the last kit reagent in the released kits, and continued, at least, in the middle of the shelf life and one month after expiry. Key stability parameters monitored for the Elecsys Anti-HCV

Summary of Safety and Effectiveness Data

Immunoassay were analytical sensitivity and results of internal control samples. Studies to characterize the stability of the Elecsys Anti-HCV Immunoassay confirm a shelf life of 12 months when stored at 2-8 °C.

Temperature stress stability studies were conducted which demonstrate stability of the anti-HCV reagent kit 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 12 human sera samples and 2 internal PreciControls in duplicate determinations. All samples fell within $\pm 20\%$ of the unstressed reference, therefore supporting stability of one week at 35°C.

On board, open reagent stability studies were performed to determine the time period for which the Elecsys Anti-HCV immunoassay kits can be kept on-board the instrument after opening. A reconstituted reagent pack was stored on-board for 72 hours at 20-25°C (onboard conditions). Twelve human sera samples and two PreciControls were tested in two-fold determination with the on-board reagent at day 1, 2, and 3. All samples fell within $\pm 20\%$ of the unstressed reference, demonstrating that the reagent kit is stable for 72 hours on-board the cobas e 601.

Stability studies were also performed to determine the time period in which Elecsys Anti-HCV immunoassay kits can be stored in the refrigerator and refrigerated on the analyzer (on-board) once opened. An Elecsys Anti-HCV reagent pack was stored for 2 weeks in the refrigerator at 2-8°C and alternately on-board at 20-25°C (onboard conditions) up to 40 hours. Each week the reagent was checked with regard to stability of the weekly calibration. A new reagent pack was opened and calibrated. Eleven human sera samples and two PreciControls were tested in duplicates with the on-board reagent at day 1, after 7 days and 14 days with weekly calibration. Recovery for each sample was calculated based on sample to cutoff index (s/co). All samples fell within $\pm 20\%$ of the unstressed reference, demonstrating that the reagent kit is stable being stored alternately in the refrigerator (up to 2 weeks) and on-board the cobas e 601 analyzer (up to 40 hours in total).

The onboard stability for open calibrators was evaluated. The studies were performed to determine the time period for which the Elecsys Anti-HCV calibrators can be kept open on-board the cobas e 601 analyzer. A new Anti-HCV reagent pack was opened and calibrated, then stored at 2-8°C. The opened calibrators were stored at 32°C (the onboard condition of the E170 rotor disk for calibration). After 2 hours of incubation at 32°C, the calibrators were tested in duplicates. All samples demonstrated $\pm 10\%$ recovery of signal. The study demonstrated that one calibration set may be used only once and the calibrators are stable for 2 hours open on-board the cobas e 601 analyzer.

Stability studies were performed to determine the time period in which the Elecsys Anti-HCV calibrators can be kept at 2 – 8°C once opened. A new reagent pack was opened and calibrated. The opened calibrators were then tested again after 2 weeks and 3 weeks when stored at 2-8°C. The calibrator stability was determined by calculation of the recovery (s/co) of opened calibrators referring to the unstressed calibrator signals. All samples demonstrated $\pm 10\%$ recovery of signal. The studies demonstrated that the calibrators are stable for 3 weeks at 2 – 8°C after first opening.

Summary of Safety and Effectiveness Data

Stability studies were performed to verify that a calibration is stable for 7 days. An Elecsys Anti-HCV reagent pack was stored for 2 weeks in the refrigerator at 2-8°C and alternately on-board at 20-25°C (up to 40 hours). Each week the reagent was checked with regard to stability of the weekly calibration. Twelve human sera samples and two PreciControls were tested in duplicates with the on-board reagent at day 1, day 7 and day 14 with weekly calibration. Recovery of each sample was calculated based on sample to cutoff index (s/co). All samples demonstrated $\pm 20\%$ recovery the unstressed reference confirming calibration stability for 7 days on the cobas e 601.

PreciControl Anti-HCV Reagent Stability:

To assess the real-time stability, whole kit samples were randomly selected from the individual lots of finished product. 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. Temperatures in the storage area were checked at predetermined intervals. The test measurement intervals started with the production date of the last kit reagent in the released kits, and continued, at least, in the middle of the shelf life and one month after expiration. The recovery of the PreciControls is calculated at every interval and compared against the initial recovery. All samples tested for PreciControl 1 demonstrated recovery of $\leq 0.25\%$ of the s/co values. For PreciControl 2 the percent recovery of the samples tested was within 80-120% of the reference. The studies confirm the stability of the Elecsys PreciControl Anti-HCV with a shelf life of 12 months when stored at 2-8 °C.

Temperature stress stability studies were conducted which demonstrate stability of the PreciControl Anti-HCV kit during transportation for one week at 35°C. A PreciControl kit was stressed for one week at 35°C. With this stressed kit, a function test was done along with a reference material (PreciControl stored at 2-8°C). To assess the stability of the Elecsys PreciControl Anti-HCV after temperature stress the cutoff indices of the PreciControls were assessed before and after incubation of the PreciControl for one week at 35°C. All samples tested for PreciControl 1 demonstrated recovery of ≤ 0.30 s/co. For PreciControl 2 the percent recovery of the samples tested was within 80-120% of the reference. The study demonstrates that Elecsys PreciControl Anti-HCV is stable for 1 week at 35°C.

Stability studies were performed to determine the time period in which the Elecsys PreciControl Anti-HCV can be kept at 2 – 8°C once opened. A new PreciControl reagent pack 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 a reference material (unstressed PreciControl at 2-8°C). All samples tested for PreciControl 1 demonstrated recovery of ≤ 0.30 s/co. For PreciControl 2 the percent recovery of the samples tested was within 80-120% of the reference. The study demonstrates that the controls are stable for 8 weeks at 2 – 8°C after first opening.

On board stability studies were performed to determine the time period in which the Elecsys PreciControl Anti-HCV can be kept open on-board the cobas e 601 analyzer. A new Anti-HCV reagent pack and a new PreciControl kit were opened and tested. The Anti-HCV reagent pack was then stored at 2-8°C and the opened PreciControls were stored at 32°C. Seven PreciControls were tested in duplicates after opened for 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, and 6 hours at 32°C. All samples demonstrated $\pm 10\%$ recovery of signal

Summary of Safety and Effectiveness Data

when compared to the unstressed reference. The studies demonstrate that the controls may be used for seven quality control events and are stable for 5 hours open on-board the cobas e 601 analyzer.

Antimicrobial Effectiveness Testing:

Antimicrobial effectiveness testing (AET) has been performed according to United States Pharmacopoeia (USP) chapter <51>. Testing was performed with all liquid reagents of Elecsys Anti-HCV. PreciControls have not been tested, because their composition is identical to Cal 1 and Cal 2, respectively.

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 is 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.

Precision:

A six-member panel run on the cobas e 601 analyzer generated the following results. The measurements were performed on one cobas e 601 analyzer, at one site, with one reagent lot, performing rackpack calibration according to instructions, spanning at least two calibrations cycles. Samples were measured in duplicate determination in two runs per day for 20 days. Repeatability and within-lab precision were calculated according to the CLSI (Clinical and Laboratory Standards Institute) guideline EP5-A2. PreciControl Anti-HCV is denoted as "PC" in the table below. Repeatability precision ranged from 2.0 to 2.8 % CV for low positive serum, moderate positive serum and PC2, and ranged from 0.007 – 0.020 SD for negative serum, high negative serum and PC1. Within-lab precision ranged from 3.3 to 5.1 % CV for low positive serum, moderate positive serum and PC2, and ranged from 0.013 – 0.036 SD for negative serum, high negative serum and PC1.

Repeatability:

Sample	Mean (s/co)	SD (s/co)	CV (%)	n
Negative serum	0.053	0.007	13.5	80
High negative serum	0.978	0.020	2.0	80
Low positive serum	1.037	0.029	2.8	80
Moderate Positive serum	2.66	0.072	2.7	80
PC 1	0.112	0.009	8.1	80
PC 2	12.37	0.245	2.0	80

Summary of Safety and Effectiveness Data

Within-Laboratory Precision:

Sample	Mean (s/co)	SD (s/co)	CV (%)	n
Negative serum	0.053	0.015	28.1	80
High negative serum	0.978	0.036	3.7	80
Low positive serum	1.037	0.053	5.1	80
Moderate Positive serum	2.66	0.119	4.5	80
PC 1	0.112	0.013	11.7	80
PC 2	12.37	0.403	3.3	80

Precision was further evaluated incorporating between-run, between-day, between-lot and between-site variation. A precision study was conducted following CLSI, EP5-A2 and EP15-A2 at three sites incorporating a seven-member panel consisting of 3 serum pools (high negative, low positive and moderately positive) and 2 controls that were assayed for 5 days, 2 runs per day, 3 replicates per run. The analysis of data was based on guidance from 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. The overall imprecision data are summarized in the following table:

Elecsys Anti-HCV system reproducibility on the cobas e 601 analyzer						
Sample		HS1 ^f	HS2 ^g	HS5 ^h	PC 1 ⁱ	PC 2 ^j
N		180	180	180	180	180
Mean	COI	0.904	1.17	2.40	0.118	15.5
	SD	0.021	0.024	0.050	0.007	0.193
Repeat-ability	% CV	2.3	2.0	2.1	6.3	1.2
	SD	0.024	0.031	0.060	0.007	0.494
Between run*	% CV	2.7	2.7	2.5	5.7	3.2
	SD	0.010	0.026	0.023	0.010	0.111
Between-day	% CV	1.2	2.3	0.9	8.8	0.7
	SD	0.030	0.058	0.119	0.013	0.987
Between-lot	% CV	3.3	5.0	4.9	10.9	6.4
	SD	0.034	0.079	0.0 ^k	0.007	0.0 ^k
Between-site	% CV	3.7	6.8	0.0	5.6	0.0
	SD	0.056	0.109	0.144	0.020	1.13
Reproducibility	% CV	6.2	9.3	6.0	17.3	7.3

- ^f) Human serum high negative
- ^g) Human serum low positive
- ^h) Human serum moderately positive
- ⁱ) PreciControl A-HCV1
- ^j) PreciControl A-HCV2

Summary of Safety and Effectiveness Data

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

*between-run = intermediate precision

Seroconversion sensitivity:

Seroconversion sensitivity of the Elecsys Anti-HCV assay has been shown by testing 20 commercial seroconversion panels in comparison to a reference anti-HCV immunoassay. For members of panels that had a reactive status in one assay earlier than the other assay, supplemental testing with the Chiron RIBA HCV 3.0 SIA was performed on the reactive panel members. The comparison of the seroconversion detection between the two assays is summarized in the following table:

Elecsys Anti-HCV - Days to Evidence of HCV Infection Seroconversion Panels								
Panel ID	Reference anti-HCV		Elecsys Anti-HCV		Chiron RIBA HCV 3.0 SIA			Difference in days to anti-HCV reactive Reference - Elecsys ^l
	Neg ^u	RX ^v	NR ^w	RX	Neg	Ind ^x	Pos	
6216	17	23	23			23		N/A
6222	36	40	26	36	36		40	4
6224	11	19	7	11	11	19		8
6226	32	37	32	37	37	39	44	0
PHV901	65	97	65	97			97	0
PHV904	7	9	2	7	7		9	2
PHV905	14	18	7	11		11	21	7
PHV906		0		0			0	0
PHV909	0	28	30			28		N/A
PHV910	4	8	4	8			8	0
PHV911	3	14	3	14			14	0
PHV912	4	7		0	4	7		7
PHV913	2	7	2	7		7		0
PHV914	12	16	9	12	12	16	24	4
PHV915	5	12	5	12			12	0
PHV917	22	85	22	85			85	0
PHV918	16	24	16	24		24	27	0
PHV919		0		0	25		28	0
PHV920	5	7	7	13			7	-6
PHV921	0	4	7	14			4	-10

^l) The dates of the first reactive test results were compared in the reference assay and Elecsys Anti-HCV assay. If the first reactive test result occurred on the same day, then the difference is 0; if Elecsys Anti-HCV assay had an earlier date, then the difference is positive; if Elecsys Anti-HCV assay had a later date, then the difference is negative.

Summary of Safety and Effectiveness Data

- u) Neg = negative
- v) RX = reactive
- w) NR = non-reactive
- x) Ind = indeterminate

The Elecsys Anti-HCV assay was reactive in the same bleed as the reference assay in 10 of the 20 panels tested. The Elecsys Anti-HCV assay was reactive earlier than the reference assay in 6 panels. The reference anti-HCV assay was reactive earlier than the Elecsys Anti-HCV assay in 2 panels. Seroconversion never occurred in either assay in 2 panels.

Genotype detection:

Testing was performed to evaluate the ability of the Elecsys Anti-HCV immunoassay on the cobas e 601 analyzer to detect antibodies to various known HCV genotypes and subtypes. Two genotyping panels from SeraCare/BBI were available for the genotype study and consisted of the following genotypes, as determined by the vendor with commercially available HCV RNA assays: 1, 2,3,4,5 and 6. The panels were tested with the Elecsys Anti-HCV assay on the cobas e 601 analyzer and the reference anti-HCV assay and final results were compared. The Elecsys Anti-HCV assay on the cobas e 601 analyzer and the reference anti-HCV assay results were in 100 % agreement for the HCV genotypes tested.

Analytical specificity:

A study was conducted to evaluate the Elecsys Anti-HCV assay for potential cross-reactivity for specimens from individuals with medical conditions unrelated to HCV infection. All specimens in the study were found to be non-reactive (negative) in the Elecsys Anti-HCV and the reference assay. Specimen results that were discordant between the two assays were sent for supplemental RIBA testing. The results are summarized in the following table:

Reactivity of the Elecsys Anti-HCV Assay in Individuals with Medical Conditions unrelated to HCV Infection					
Category	n	Anti-HCV reference assay			
		Negative	Reactive		
		Elecsys Anti-HCV assay		NR ^u	RX ^v
Anti-nuclear antibody (ANA)	10	9	0	0	1
Cytomegalovirus (anti-CMV positive)	10	10	0	0	0
Dengue Fever	10	10	0	0	0
Elevated IgG	10	10	0	0	0
Elevated IgM	10	10	0	0	0
Elevated total bilirubin	10	8	0	1 ^p	1
Elevated total protein	10	8	0	0	2
Epstein-Barr Virus (anti-EBV positive)	10	10	0	0	0
<i>Escherichia coli</i> (<i>E. coli</i>)	10	8	0	0	2

Summary of Safety and Effectiveness Data

HAV vaccination	10	10	0	0	0
HBV vaccination	10	10	0	0	0
Hepatitis A Virus (anti-HAV positive)	10	10	0	0	0
Hepatitis B Virus (anti-HBV positive)	10	9	0	1 ^p	0
Hepatitis D Virus (anti-HDV positive)	11	5	3 ^q	0	3
Hepatitis E Virus (anti-HEV positive)	40	4	5 ^r	1 ^p	30
Herpes Simplex Virus (HSV) IgG	10	10	0	0	0
Human immunodeficiency Virus (anti-HIV-1 positive)	10	9	0	0	1
Human T-cell Lymphotropic Virus (HTLV)	10	8	1 ^s	0	1
Influenza vaccine recipients	10	10	0	0	0
Multiparous female	10	10	0	0	0
Murray valley / Australian encephalitis	2	2	0	0	0
Non-viral liver disease	17	16	0	0	1
Parvovirus B ₁₉ infection	10	9	0	0	1
Rheumatoid Factor positive	10	9	0	0	1
Rubella	10	9	1 ^p	0	0
Syphilis (T. pallidum)	10	9	0	1 ^p	0
Systemic lupus erythematosus (SLE)	10	10	0	0	0
Toxoplasmosis IgG positive	10	9	0	0	1
Varicella zoster (VZV)	10	9	0	1 ^p	0
West Nile virus infection	11	11	0	0	0
Yeast infection	10	9	0	0	1

ⁿ⁾ NR = non-reactive

^{o)} RX = reactive

^{p)} RIBA testing resolved results in favor of Elecsys assay

^{q)} 2 RIBA testing resolved in favor of reference assay, 1 RIBA was indeterminate

^{r)} 4 RIBA testing resolved in favor of reference assay, 1 RIBA was indeterminate

^{s)} RIBA testing resolved results in favor of reference assay

False positive results were observed in a limited number of patients positive for HBsAg. Studies also show there is the potential for cross-reactivity from patients with antibodies to Hepatitis D Virus or Hepatitis E Virus. The appropriate limitation appears in the package insert.

Seroconversion sensitivity:

Seroconversion sensitivity of the Elecsys Anti-HCV assay has been shown by testing 20 commercial seroconversion panels in comparison to a reference anti-HCV immunoassay. For members of panels that had a reactive status in one assay earlier than the other assay, supplemental testing with the Chiron RIBA HCV 3.0 SIA was performed on the reactive

Summary of Safety and Effectiveness Data

panel members. The comparison of the seroconversion detection between the two assays is summarized in the following table:

Elecsys Anti-HCV - Days to Evidence of HCV Infection Seroconversion Panels								
Panel ID	Reference anti-HCV		Elecsys Anti-HCV		Chiron RIBA HCV 3.0 SIA			Difference in days to anti-HCV reactive Reference - Elecsys [†]
	Neg ^u	RX ^v	NR ^w	RX	Neg	Ind ^x	Pos	
6216	17	23	23			23		N/A
6222	36	40	26	36	36		40	4
6224	11	19	7	11	11	19		8
6226	32	37	32	37	37	39	44	0
PHV901	65	97	65	97			97	0
PHV904	7	9	2	7	7		9	2
PHV905	14	18	7	11		11	21	7
PHV906		0		0			0	0
PHV909	0	28	30			28		N/A
PHV910	4	8	4	8			8	0
PHV911	3	14	3	14			14	0
PHV912	4	7		0	4	7		7
PHV913	2	7	2	7		7		0
PHV914	12	16	9	12	12	16	24	4
PHV915	5	12	5	12			12	0
PHV917	22	85	22	85			85	0
PHV918	16	24	16	24		24	27	0
PHV919		0		0	25		28	0
PHV920	5	7	7	13			7	-6
PHV921	0	4	7	14			4	-10

[†] The dates of the first reactive test results were compared in the reference assay and Elecsys Anti-HCV assay. If the first reactive test result occurred on the same day, then the difference is 0; if Elecsys Anti-HCV assay had an earlier date, then the difference is positive; if Elecsys Anti-HCV assay had a later date, then the difference is negative.

^u) Neg = negative

^v) RX = reactive

^w) NR = non-reactive

^x) Ind = indeterminate

The Elecsys Anti-HCV assay was reactive in the same bleed as the reference assay in 10 of the 20 panels tested. The Elecsys Anti-HCV assay was reactive earlier than the reference assay in 6 panels. The reference anti-HCV assay was reactive earlier than the Elecsys Anti-HCV assay in 2 panels. Seroconversion never occurred in either assay in 2 panels.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

To evaluate the Elecsys Anti-HCV assay's ability to detect anti-HCV antibody 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 of the Elecsys Anti-HCV assay on the cobas e 601 immunoassay analyzer.

The study population included individuals with specific risks or history associated with HCV infection. Medical/clinical risks include transfusions or transplants, recipients of clotting factors (hemophiliacs), HIV infected or immunocompromised, dialysis patients, prenatal exposure, and a family history of any hepatitis. Occupational risks include healthcare workers, tattoo artists, morticians and individuals with history of incarceration. Sexual risks include individuals with multiple sex partners, individuals sharing sex with STDs diagnosed partner(s), male-on-male sex partners, individuals sharing sex with HIV-infected partner(s), commercial sex workers. Behavioral risks include IV drug users (current or past), individuals sharing straw cocaine, and individuals with tattoo or body piercing. Also included were individuals with signs or symptoms (subjects must have clinical symptoms or laboratory data or histological findings suggestive for hepatitis infection).

The signs and symptoms population includes subjects that are hepatic (jaundice, discoloration of urine or stool), subjects with non-specific GI (nausea, vomiting), subjects with flu-like symptoms (fatigue, fever, arthralgias), subjects with laboratory values (elevated ALT, AST, bilirubin) suggestive for liver disease, subjects with extrahepatic disease possibly associated with HCV (cryoglobulinemia, lymphoma, autoimmune thyroiditis, renal disease, dermatologic conditions such as lichen planus and porphyria cutanea tarda), and subjects with histological findings suggestive for liver disease, if available. The signs and symptoms population also must belong to one of the listed increased risk behaviors for HCV groups.

Specimens were obtained from 2206 subjects prospectively enrolled at seven sites located in 4 geographic regions of the USA. Of the 2,206 subjects approximately 50% were enrolled in California, 43% in Florida, 5% in New Jersey and 2% in Georgia. Of these, 2094 were available for testing and analysis. 103 at risk and 6 symptomatic subjects were dropped due to subject discontinuation or exclusion criteria

The group was; Caucasian (50.3%), African American (47.8%), American Indian/Alaska Native (0.62%), Asian (0.33%), Pacific Islander (0.24%), with the remaining 0.72% represented by other ethnic groups. Of the 2094 at risk subjects, 609 (29.0 %) were female and 1488 (71.0 %) were male. The mean age of the subjects was 43 years (age range: 21 to 81 years). The HCV status for each subject was determined from the results of a reference assay, Vitros Anti-HCV Assay on the Vitros ECi/ECiQ Immunodiagnostic System, for the detection of immunoglobulin G antibody (IgG) to hepatitis C virus, and the Chiron**RIBA**HCV 3.0 SIA, when required. In addition, reference assays for HBsAg, HBsAg Confirmatory, and was performed to determine co-infection with HBV. All reference testing during the clinical laboratory study was performed following manufacturer's instructions using assays previously licensed or approved by the FDA. Elecsys Anti-HCV testing of these specimens occurred at 3 clinical testing sites located in St. Louis, MO, Ft. Lauderdale, FL and South Bend, IN.

Summary of Safety and Effectiveness Data

Approximately 61.2% (1283/2094) of the study subjects participating in the Elecsys Anti-HCV clinical study were at risk for HCV but reported no recent or current signs or symptoms of hepatitis.

The ethnic distribution of this group was as follows; African American (50.7%), Caucasian (47.2%), American Indian/Alaska Native (0.70%), Asian (0.23%), Pacific Islander (0.23%), and the remaining 0.86% represented by other ethnic groups. The group was 69.5% male and 30.5% female and ranged in age from 21 to 81 years. All were at risk for viral hepatitis or HCV infection due to lifestyle, behavior, occupation or known exposure event, or belonged to clinical groups at risk for HCV infection.

A. Distribution of Results

Expected Results:

The distribution of the Elecsys Anti-HCV reactive and negative results among the study subjects at risk of hepatitis by age and gender are presented in the following table.

Expected Results for the Elecsys Anti-HCV Assay in Study Subjects At Risk of HCV infection

Age Group (Years)	Gender	Elecsys Anti-HCV Result		Total (n)
		Reactive n (%)	Non-Reactive n (%)	
21 to 29	Female	1 (0.93)	107 (99.07)	108
	Male	4 (4.49)	85 (95.51)	89
30 to 39	Female	4 (4.65)	82 (95.35)	86
	Male	24 (13.26)	157 (86.74)	181
40 to 49	Female	25 (22.32)	87 (77.68)	112
	Male	73 (20.45)	284 (79.55)	357
50 to 59	Female	26 (37.14)	44 (62.86)	70
	Male	95 (42.04)	131 (57.96)	226
60 to 69	Female	6 (60.00)	4 (40.00)	10
	Male	11 (32.35)	23 (67.65)	34
70 to 79	Female	0 (0.00)	4 (100.00)	4
	Male	0 (0.00)	5 (100.00)	5
80 to 89	Female	0 (0.00)	1 (100.00)	1
	Male	0 (0.00)	0 (0.00)	0
Total		269 (20.97)	1014 (79.03)	1283

Summary of Safety and Effectiveness Data

Expected Results for the Elecsys Anti-HCV Assay in Study Subjects with Signs or Symptoms of Hepatitis

		Elecsys Anti-HCV Result		
Age Group (Years)	Gender	Reactive n (%)	Non-Reactive n (%)	Total (n)
21 to 29	Female	4 (8.00)	46 (92.00)	50
	Male	9 (12.68)	62 (87.32)	71
30 to 39	Female	4 (7.84)	47 (92.16)	51
	Male	11 (11.70)	83 (88.30)	94
40 to 49	Female	23 (36.51)	40 (63.49)	63
	Male	63 (29.03)	154 (70.97)	217
50 to 59	Female	14 (31.11)	31 (68.89)	45
	Male	96 (56.14)	75 (43.86)	171
60 to 69	Female	1 (16.67)	5 (83.33)	6
	Male	15 (38.46)	24 (61.54)	39
70 to 79	Female	0 (0.00)	3 (100.00)	3
	Male	0 (0.00)	1 (100.00)	1
80 to 89	Female	0 (0.00)	0 (0.00)	0
	Male	0 (0.00)	0 (0.00)	0
Total		240 (29.59)	571 (70.41)	811

B. Results by Specimen Classification

Following testing with the reference anti-HCV assay and supplemental testing with the Chiron* RIBA* HCV 3.0 SIA where indicated, 2094 subjects were assigned an HCV status of HCV infected or not HCV infected based on the final results obtained with both assays as required. The HCV status of the remaining 36 subjects could not be determined due to indeterminate results with the Chiron* RIBA* HCV 3.0 SIA. Assignment of HCV status is presented in the following table.

HCV Status Algorithm				
Reference anti-HCV final test result	Chiron RIBA HCV 3.0 SIA	Indeterminate HCV status	COBAS AMPLICOR Hepatitis C Virus Test, Version 2.0	HCV status
Reactive	Indeterminate	Not determined	Negative	Not HCV infected*
Reactive	Indeterminate	Not determined	Positive	HCV infected
Negative	Not applicable	Not HCV infected	Not applicable	Not HCV infected
Reactive	Positive	HCV infected	Not applicable	HCV infected
Reactive	Negative	Not HCV infected	Not applicable	Not HCV infected

* Negative test result does not exclude the possibility of exposure to hepatitis C virus

Summary of Safety and Effectiveness Data

The following table compares the Elecsys Anti-HCV results with HCV status according to a ranking of the risk of HCV infection in study subjects (n=2094). The ranking was based on a clinical evaluation of the chances of acquiring the disease through the following modes of transmission, with the most common given higher rankings. Each patient was assigned only one risk (the highest). Assignment of HCV status was according to the algorithm presented in the previous table. "Intermediate HCV Status" is based on RIBA testing.

Comparison of the Elecsys Anti-HCV Results to HCV Status
For the Prospective Population by Presumptive Diagnosis and Risk Groups for HCV

Hepatitis Rank Risk Group ^o	Intermediate HCV Status						Total
	HCV Infected		Not Determined		HCV Not Infected		
	Elecsys Anti-HCV Result		Elecsys Anti-HCV Result		Elecsys Anti-HCV Result		
	NR ^p (n)	RX ^q (n)	NR (n)	RX (n)	NR (n)	RX (n)	
Signs and Symptoms	0	214	2	14	569	12	811
Recipients of clotting factor	0	3	0	0	8	2	13
User of IV drugs	0	100	1	6	80	2	189
Dialysis	0	1	0	0	7	1	9
Transfusion/Transplant	0	14	0	3	31	0	48
High Risk Sex	1	75	1	6	557	6	646
Healthcare Worker	0	7	0	1	63	0	71
Other Lower Rank ^r	0	36	1	1	259	3	300
Other Unranked ^s	0	1	0	0	5	1	7
Total	1	451	5	31	1579	27	2094

^o - Individuals with increased risk of HCV infection
^p - Non-Reactive
^q - Reactive
^r - Risk ranked lower than top six risks.
^s - risk provided by subject that was not predefined in the CRF.

The HCV status of 36 subjects could not be determined following testing with the reference anti-HCV assay (all were repeatedly reactive) and the Chiron* RIBA* HCV 3.0 SIA (all had indeterminate results); therefore the HCV status for the subjects was considered not determined. Additional supplemental testing for HCV RNA by PCR was performed on the 36 samples using the COBAS AMPLICOR™ Hepatitis C Virus Test, version 2.0 (Roche Molecular Systems, Inc.). The results of this testing provided the basis for the final HCV status determination of the 36 samples following supplemental PCR testing and are presented in the following table.

Summary of Safety and Effectiveness Data

Determination of the Final HCV Status following HCV-RNA Testing

Hepatitis Ranked Risk Group	Samples (n)	HCV-RNA Result	Elecsys Anti-HCV Result	HCV Status Following HCV-RNA
Signs and Symptoms	8	Detected	RX	HCV Positive
	2	Not Detected	NR	HCV Negative
	6	Not Detected	RX	HCV Negative
User of IV drugs (current or past)	1	Detected	RX	HCV Positive
	1	Not Detected	NR	HCV Negative
	5	Not Detected	RX	HCV Negative
Transfusion/Transplant	3	Not Detected	RX	HCV Negative
High Risk Sex	1	Detected	NR	HCV Positive
	2	Detected	RX	HCV Positive
	4	Not Detected	RX	HCV Negative
Healthcare Worker	1	Not Detected	RX	HCV Negative
Other	1	Not Detected	NR	HCV Negative
	1	Not Detected	RX	HCV Negative
Total	36			

C. Percent Agreement

Percent positive and percent negative agreement between the Elecsys Anti-HCV assay on the cobas e 601 analyzer and HCV status were calculated for both symptomatic and asymptomatic subjects with various risks for HCV infection, and for the overall study population (N=2094). The table below summarizes these calculations and provides the upper and lower 95% exact confidence intervals.

Summary of Safety and Effectiveness Data

Elecsys Anti-HCV Results versus the Final HCV Status: Percent Agreement among Study Subjects Ranked According to Risk for HCV Infection

Hepatitis Ranked Risk Group	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Signs and Symptoms	100.00 (222/222)	98.35-100.00	96.94 (571/589)	95.21-98.18
Recipients of clotting factor	100.00 (3/3)	29.24-100.00	80.00 (8/10)	44.39-97.48
User of IV drugs (current or past)	100.00 (101/101)	96.41-100.00	92.05 (81/88)	84.30-96.74
Dialysis	100.00 (1/1)	2.50-100.00	87.50 (7/8)	47.35-99.68
Transfusion/Transplant	100.00 (14/14)	76.84-100.00	91.18 (31/34)	76.32-98.14
High Risk Sex	97.47 (77/79)	91.15-99.69	98.24 (557/567)	96.78-99.15
Healthcare Worker	100.00 (7/7)	59.04-100.00	98.44 (63/64)	91.60-99.96
Other Lower Rank ^t	100.00 (36/36)	90.26-100.00	98.48 (260/264)	96.17-99.59
Other Unranked ^u	100.00 (1/1)	2.50-100.00	83.33 (5/6)	35.88-99.58
Total	99.57 (462/464)	98.45-99.95	97.12 (1583/1630)	96.18-97.87

^t - Risk ranked lower than top six risks.
^u - risk provided by subject that was not predefined in the CRF.

The percent positive agreement with HCV final status was determined by dividing the number of reactive Elecsys Anti-HCV assay results by the total number of subjects determined to be 'HCV Infected' by the combination of the anti-HCV reference assay, RIBA and PCR. The percent negative agreement with HCV status was determined by dividing the number of negative Elecsys Anti-HCV assay results by the number of subjects determined to be 'Not HCV Infected'.

The positive percent agreement between the Elecsys Anti-HCV assay results and the HCV Infected status for the overall population (n = 2094) base was 99.6 % (462/464 with a 95 % confidence interval of 98.5 % to 99.95 %. The negative percent agreement between the Elecsys Anti-HCV assay results and the Not HCV Infected status for the overall population (n = 2094) was 97.1 % (1583/1630) with a 95 % confidence interval of 96.2 % to 97.9 %.

The positive percent agreement between the Elecsys Anti-HCV assay results and the HCV Infected status for the symptomatic study population (n = 811) was 100 % (222/222) with a 95 % confidence interval of 98.4 % to 100 %. The negative percent agreement between the Elecsys Anti-HCV assay results and the Not HCV Infected status was 96.9 % (571/589) with a 95 % confidence interval of 95.2 % to 98.2 %.

The positive percent agreement between the Elecsys Anti-HCV assay results and the HCV Infected status for the at risk population (n = 1283) was 99.2 % (240/242). The negative percent agreement between the Elecsys Anti-HCV assay results and the Not HCV Infected status was 97.2 % (1012/1041) with a 95 % confidence interval of 96.0 % to 98.1 %.

Summary of Safety and Effectiveness Data

D. Potential Cross-Reactivity with HBV Co-infected Individuals

Potential Cross reactivity with HBV infected individuals:

Samples were tested for Hepatitis B infection (HBV) in a population of 2094 prospectively collected samples. HBV positive samples (n = 55) were identified in 2094 tested samples. Hepatitis B infection was determined by commercially available HBsAg and HBsAg Confirmatory assays. The table below compares the Elecsys Anti-HCV assay results with HCV status according to the ranking of the risk of HCV infection in these study subjects.

Elecsys Anti-HCV Results versus the Final HCV Status: Percent Agreement among HBV Positive Study Subjects Ranked According to Risk for HCV Infection

Hepatitis Rank Risk Group ^x	Final HCV Status				Total
	HCV Positive		HCV Negative		
	Elecsys Anti-HCV Result		Elecsys Anti-HCV Result		
	NR ^y (n)	RX ^z (n)	NR (n)	RX (n)	
Signs and Symptoms	0	5	11	0	16
User of IV drugs (current or past)	0	2	1	1	4
Transfusion/Transplant	0	1	1	0	2
High Risk Sex	0	3	18	4	25
Healthcare Worker	0	1	0	0	1
Other Ranked ^{aa}	0	0	6	0	6
Other Not Ranked ^{ab}	0	0	1	0	1
Total	0	12	38	5	55
^x - Individuals with increased risk of HCV infection ^y - Non-Reactive ^z - Reactive ^{aa} - Individuals with increased risk ranked lower than top 6 risks. ^{ab} - Individuals with increased risk provided by subject that is not predefined in CRF.					

Fifty five samples were infected with HBV. Twelve samples had evidence of a HCV-HBV co-infection. Positive percent agreement between Elecsys and the reference was 100% (12/12); negative percent agreement between the same assays was 88.37% (38/43). Of the five samples that tested reactive for final status while the Elecsys Anti-HCV assay tested non-reactive, four Elecsys Anti-HCV reactive subjects had RIBA indeterminate/RNA negative profiles, and one subject had RIBA negative results. An explanation for indeterminate RIBA/HCV-RNA negative profiles are either past cleared infection representing long lasting residual antibody (to c22p and c33c) or nonspecific “false” reactivity (to c33c and NS5). Early seroconversion with undetectable HCV-RNA also cannot be excluded. Finally, Roche demonstrated with a specificity study with 10 HBsAg positive samples that no cross-reactivity took place with using the Elecsys Anti-HCV assay.

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

As a diagnostic test, the Elecsys Anti-HCV 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. There were no adverse effects of the device reported while the study was conducted. The benefits of the HCV Assay outweigh the risks.

B. Effectiveness Conclusions

Multicenter clinical studies were conducted in the US. The Elecsys Anti-HCV Immunoassay used on Cobas e 601 performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

1. The positive percent agreement between the Elecsys Anti-HCV assay results and the HCV Infected status for the at-risk and symptomatic populations (n = 2097) was 99.6 % (463/465) with a 95 % confidence interval of 98.5 % to 99.95 %. The negative percent agreement between the Elecsys Anti-HCV assay results and the Not HCV Infected status was 96.9 % (1581/1632) with a 95 % confidence interval of 95.9 % to 97.7 %.
2. The comparison of the performance of the Elecsys Anti-HCV assay to the HCV status of the patients in the study, calculated for patients with signs or symptoms of hepatitis, resulted in a positive percent agreement of 100%, with a 95% exact confidence interval of 98.4 to 100.00% and a negative percent agreement of 96.8%, with a 95% confidence of 95.0 to 98.1%.
3. The comparison of the performance of the Elecsys Anti-HCV assay to the HCV status calculated for patients at risk of hepatitis C infection, resulted in a positive percent agreement of 99.2% and a negative percent agreement of 96.9%.
4. The ability of the Elecsys Anti-HCV Assay to detect HCV antibodies in infected individuals was demonstrated by seroconversion panel evaluation. Seroconversion sensitivity of the Elecsys Anti-HCV assay has been shown to be acceptable by testing 20 commercial seroconversion panels in comparison to a reference anti-HCV immunoassay.

Summary of Safety and Effectiveness Data

5. The evaluation of genotype panels demonstrated that the Elecsys Anti-HCV assay recognizes antibodies to various known hepatitis C virus genotypes and subtypes. The following genotypes were included and recognized in the panels tested: 1, 2,3,4,5, and 6
6. Analytical specificity studies evaluated the potential cross reactivity with antibodies to other viral and bacterial infections. It has been shown that the device has no significant cross-reactivity with viruses or organisms that may cause similar symptoms or are closely related to HCV. Limited cross-reactivity has been observed with individuals with antibodies to hepatitis B, D and E viruses.
7. Among the 464 patients enrolled in the study who were determined to be HCV positive by the reference method (final HCV status), 55 were identified to be reactive for HBsAg. The overall positive percent agreement between the Elecsys Anti-HCV assay and the final HCV infected status in those patients was 100.00% (12/12). The overall negative percent agreement between the Elecsys Anti-HCV assay and the final HCV infected status in those patients was 88.37% (38/43).
8. Acceptable performance was demonstrated with the Elecsys Anti-HCV assay when testing specimens collected in serum or plasma (potassium EDTA, lithium heparin and sodium heparin).
9. The Elecsys Anti-HCV assay demonstrated an acceptable between site reproducibility based on within-run, between run, day, lot and site (pooled data from the three sites) of 5.2 to 7.7%. The individual precision estimates for the different components of variance by site were: <5% for within run, <4% between day, <6% between lot, <3% between site

The results from both the non-clinical and clinical studies indicate that the Elecsys Anti-HCV assay is effective for the qualitative in vitro determination of antibodies to HCV in human serum and plasma. The Elecsys Anti-HCV assay may be used, in conjunction with other laboratory results and clinical information, to aid in the presumptive diagnosis of HCV infection in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis C infection. The test does not determine the state of infection or associated disease.

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. Based on the results from both the non-clinical and clinical studies, the Elecsys Anti-HCV assay when used according to the provided directions and in conjunction with other laboratory results and clinical information, is safe and effective for the qualitative in vitro determination of antibodies to HCV in human serum and plasma and poses minimal risk to the patient due to false test results. The Elecsys Anti-HCV assay may be used, in conjunction with other laboratory results and clinical

Summary of Safety and Effectiveness Data

information, to aid in the presumptive diagnosis of HCV infection in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis C infection. The test does not determine the state of infection or associated disease. This device should benefit the physician to aid in the diagnosis of HCV.

XIII. CDRH DECISION

CDRH issued an approval order on April 29, 2010.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

None

Summary of Safety and Effectiveness Data