SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: Elecsys® Anti-HCV Immunoassay and
Elecsys® PreciControl Anti-HCV on cobas e 411

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: P090007

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 411 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 411 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.
- 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 411 Immunoassay Analyzer labeling.

V. DEVICE DESCRIPTION

A. Kit Configuration and Components

1. The Elecsys® Anti-HCV Immunoassay consists of nine reagents:

   - 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.

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

B. Assay Principle

Elecsys® Anti-HCV Immunoassay

The Elecsys® Anti-HCV Immunoassay is an *in vitro* qualitative, two-step double antigen sandwich assay designed to detect anti-HCV antibodies in human serum or plasma. The assay is based on the electrochemiluminescence immunoassay technology (ECLIA) where streptavidin-coated microparticles are used to capture the antigen-antibody complexes. The test utilizes three recombinant antigens derived from core and non-structural (NS3 and NS4) regions of the virus. The system consists of one reagent with HCV antigens conjugated with biotin and another reagent with the antigens labeled with a ruthenium complex. In the first step, 40 µL of sample is incubated with 60 µL of a reagent containing biotinylated HCV antigens and 60 µL of a reagent containing HCV antigens labeled with a ruthenium complex. Any anti-HCV antibodies present in the sample will react with the antigens present in the reagents to form a "sandwich" antigen-antibody complex. In the second step, streptavidin-coated microparticles are added to the mixture. During the second incubation interval, the antigen-antibody complexes are captured by the microparticles via the interaction of biotin and streptavidin. Next, the reaction mixture is aspirated and transferred into a measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Liquid flow rinses away any remaining unbound substances. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier tube. Results are determined automatically by the Elecsys® software by comparing the signal obtained from the sample with the cutoff value obtained by calibration with an anti-HCV calibrator. The total duration of the assay is 18 minutes.

Elecsys® PreciControl Anti-HCV

The PreciControl Anti-HCV is used for monitoring the performance of the Elecsys® Anti-HCV Immunoassay and consists of two reagents. PreciControl Anti-HCV 1 contains human serum, anti-HCV negative, whereas PreciControl Anti-HCV 2 reagent is positive for human anti-HCV at a low positive concentration.

C. 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 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 Results

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.

Final Elecsys Anti-HCV Assay Results

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 known 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

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assay (SIA) and/or polymerase chain reaction (PCR) for detection of HCV RNA) to determine inactive or resolved infection versus active HCV replication.' 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, 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 411. The studies are described below.

A. Cut-off Determination

The cut-off value was established with in-house studies by measuring a panel of 1144 samples, including seroconversion panels, samples from dialysis patients, pregnant women, potentially cross-reactive samples, anti-HCV positive samples, blood donor samples and samples from commercial performance panel including different genotypes. A Receiver Operator Curve (ROC) analysis was used to optimize sensitivity and specificity.

Validation of the cut off was performed by external clinical studies.

B. Endogenous Interference

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 serum sample were spiked with each of the potentially interfering substances. Each interferent was evaluated at 10 concentrations. All samples were tested in duplicate. The acceptance criteria were set at +/- 20% (s/co) average recovery of anti-HCV for samples ≥1.0 (s/c) and at +/- 0.2 s/co for samples < 1.0 s/c, when compared with initial un-spiked results.

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 Elecsys® Anti-HCV assay.

The study demonstrated no interference from bilirubin up to 50 mg/dL, lipemia up to 2100 mg/dL, biotin up to 50 ng/mL, and total protein up to 12.0 g/dL.

C. Drug Interferences

A drug interference study was performed on the cobas e 411 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*.

D. 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. Forty matched pairs were collected in the evaluation of each: serum/gel separation tubes, Lithium heparin plasma, K_2-EDTA plasma, sodium heparin plasma and sodium citrate plasma. The samples were spiked with anti-HCV levels to obtain relevant concentrations (negative-no spiking, high-negative, low-positive and positive). All samples were assayed in triplicate. Recovery of each plasma sample relative to the corresponding serum was calculated.

The studies support the use of plasma collected using blood collection tubes containing the following anticoagulants: K_2-EDTA, sodium heparin, and lithium heparin. The data also showed that serum-gel separation tubes do not interfere with the Elecsys® Anti-HCV assay.

The studies revealed that the sodium citrate plasma tubes are not suitable for use with the Elecsys® Anti-HCV assay. The appropriate limitation appears in the package insert.

E. Carryover Study

The cobas e 411 analyzer uses disposable tips for sample and reagent pipetting which excludes any risk of carryover by design. However, the samples pass through the measuring cell and there is a potential for residual signal (bead) carryover. A study was performed to determine the extent of signal carryover for the Elecsys® Anti-HCV on the cobas e 411 in the measuring cell. Seven individual negative anti-HCV samples were analyzed alternately with samples tested for Toxo-IgG. The Elecsys Toxo-IgG assay was selected because it generates a very high signal. The deviation of the first signal value of the negative sample after the high-signal-generating sample was compared to the median signal of the triplicate measurements before testing the high-signal-generating sample. The observed deviation in counts recovery ranged from -1% to 4%.

F. High Dose Hook Effect

A study was performed to give evidence that a high dose hook effect does not lead to false negative results. Three high titer positive samples were diluted 3-fold 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 Elecsys® Anti-HCV assay. Thus no false negative results due to high dose hook effect are observed.

G. Stability Studies

1. Sample Stability

Studies were conducted to evaluate the stability of patient samples under three different storage conditions. Twelve anti-HCV serum samples (negative, high negative, low positive and positive) were stored at -20°C, at 2-8°C and at 25°C. The time points tested were day 0 (unstressed), 2 days, 7 days, 14 days, and 21 days for storage stability at 2-8°C. The time points tested for storage stability at 25°C were day 0 (unstressed), day 1, day 2, day 3 and day 4. The time points tested for storage stability at -20°C were time 0 (unstressed) and 3 months. Additionally, sample stability was evaluated under repeated freeze/thaw conditions. Time points tested for the 6 freeze/thaw cycles were time 0 (unstressed) and after each freeze/thaw cycle. Recovery at each time point was calculated based on sample to cut-off index. The studies demonstrated that serum samples may be stored for 3 months at –20 °C, 21 days at 2-8 °C, 4 days at 25°C, and may be subjected up to 6 freeze/thaw cycles prior to testing with the Elecsys Anti-HCV Immunoassay without loss of anti-HCV.

2. Elecsys Anti-HCV Immunoassay Reagent Stability Studies

i. Real Time (Shelf Life) Stability

To assess the real-time stability of the Elecsys Anti-HCV reagents, three whole kits 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 date. Key stability parameters monitored for the Elecsys® Anti-HCV Immunoassay were analytical sensitivity and results of internal control samples. Stability studies conducted on of three lots of reagents demonstrate a shelf life stability

of the Elecsys® Anti-HCV Immunoassay for 15 months when stored at 2-8 °C.

ii. Temperature Stress Stability (Transport Stability)

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 ± 20% of the unstressed reference, therefore supporting stability of one week at 35°C.

iii. On-Board Stability – Open Reagent Pack

Stability studies were conducted to determine the length of time that the Elecsys® Anti-HCV immunoassay kits can be kept on-board the instrument once opened. A reconstituted Elecsys Anti-HCV rack-pack was stored on-board of the cobas e 411 analyzer for 72 hours at 20°C±3°C. The assay was calibrated at day 0 and was not recalibrated during the study. Twelve human serum samples (negative, high negative, low positive and positive) and two PreciControls were tested in two-fold determinations at day 0, 1, 2, and 3. Recovery for each sample was calculated based on the sample to cutoff index (s/co) relative to the result on day 0 for the corresponding sample. All results met the predetermined acceptance criteria. The data support the reagent stability on-board of cobas e 411 for 72 hours.

iv. On-Board Stability – Open Reagent Pack (On-Board/Refrigerated)

Stability studies were performed to determine the time period in which Elecsys® Anti-HCV immunoassay kits can be stored alternately in the refrigerator and on the analyzer (on-board) once opened. An Elecsys Anti-HCV rack-pack was stored for 2 weeks in the refrigerator at 2-8°C and alternately on-board at 20°C ±3°C (up to 40 hours). Each week the reagent was checked for stability against the weekly calibration. Each calibration was performed with a new reagent pack. Twelve human serum samples (negative, high negative, low positive and positive) and two PreciControls were tested in duplicates with the on-board reagent at day 0, after 7 days and after 14 days. Recovery for each sample was calculated based on the sample to cutoff index (s/co) relative to the result on day 0 for the corresponding sample. All results met the predetermined acceptance criteria. The data support Elecsys Anti-HCV reagent stability when stored alternately in the refrigerator (up to 2 weeks) and on-board the cobas e 411 analyzer (up to 40 hours in total).

3. Calibrator Stability

i. On-Board Stability – Open Calibrators

Stability studies were performed to determine the time period in which the Elecsys® Anti-HCV calibrators can be kept open on-board the cobas e 411 analyzer (20-25°C). A new Anti-HCV reagent pack was opened and calibrated, then stored at 2 - 8°C. Seven calibrators were opened and stored at 25°C. The calibrators were tested in duplicates after the different time intervals in one run. Recovery for each calibrator was calculated based on counts (signal). The results met the predetermined acceptance criterion of 90 - 110% recovery of counts (signal) after 5 hours at 25°C and support a maximum of five calibration events (five one-hour intervals) on the cobas e 411 analyzer.

ii. Calibrator Stability After Opening

Stability studies were conducted 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 placed in a refrigerator at 2 - 8°C then tested again after 2 and 3 weeks, in duplicates. The calibrator stability was determined by calculation of the signal recovery (counts) of opened calibrators when compared to the signal obtained on the day of the calibration (unstressed). The data demonstrate that the calibrators are stable for 2 weeks at 2 – 8°C after opening.

iii. Calibration Interval Stability Studies

A stability study was performed to verify the claim that a calibration is stable for 7 days on the cobas e 411 instrument. An Elecsys Anti-HCV rack-pack was stored for 2 weeks in the refrigerator at 2 - 8°C and alternately on-board at 20°C±3°C (up to 40 hours) to simulate on-board stress. Each week the reagent was checked for stability of the weekly calibration. A new reagent pack was opened and calibrated. Twelve human serum samples (negative, high negative, low positive and positive) and two PreciControls were tested in duplicates with the on-board reagent on day 0, after 7 days and after 14 days. Recovery for each sample was calculated based on sample to cutoff index (s/co). The results of the study support calibration stability on the cobas e 411 of 7 days.

4. PreciControl Anti-HCV Stability Studies

i. Real-Time (Shelf Life) 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. 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. The recovery of the PreciControls is calculated at every interval and compared against the initial recovery. Studies to characterize the stability of the Elecsys® PreciControl Anti-HCV confirm a shelf life of 15 months when stored at 2-8°C.

ii. Temperature Stress Stability (Transport Stability)

Temperature stress stability studies were conducted to demonstrate stability of the PreciControl Anti-HCV kit during transportation for one week at 35°C. A PreciControl reagent kit was placed at 35°C for one week and then returned to refrigerator. To assess the stability of the Elecsys PreciControl Anti-HCV reagent after temperature stress, the cutoff indices of the PreciControls were assessed in duplicates before and after incubation of PreciControls for one week at 35°C. The data supported stability of the reagents for one week under the stress conditions.

iii. Stability after Opening

Stability studies were performed to determine the length of the stability interval of the Elecsys® PreciControl Anti-HCV when stored at 2 – 8°C once opened. A new PreciControl reagent pack was opened and tested, then placed at 2 - 8°C for 9 weeks. The reagent was tested after 4, 8, and 9 weeks in duplicates along with a freshly opened material. The results of the study demonstrated stability of the Elecsys® PreciControl Anti-HCV for 9 weeks after opening, when stored at 2 – 8°C.

iv. On-Board Stability – Open PreciControls

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 411 analyzer. When the PreciControls are on-board the analyzer, the on-board temperature the PreciControls are exposed to is 20-25°C. A new PreciControl reagent pack was opened and tested, then placed at 25°C to simulate on-board conditions. The stressed PreciControls were tested on the cobas e 411 in duplicates in one-hour intervals for 6 hours. The recovery at each interval was

compared to that at point 0 hours. The data support on-board stability of the Elecsys® PreciControl Anti-HCV for at least 5 hours.

H. 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. 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. The results demonstrated that the preservation of all reagents was effective and met the USP criteria.

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. There has been no microbial growth observed in the components stored at elevated temperatures, relative to recommended 2 - 8° C storage, in previous accelerated stability studies.

I. Precision

A precision study was conducted in-house to evaluate the repeatability (within-run) and within-lab precision of the Elecsys Anti-HCV assay. A six-member panel, consisting of 4 human sera (one moderate positive, one negative, one low positive and one high negative) and two PreciControls (one positive and one negative) was measured in duplicate determinations in two runs per day for 20 days (n=80). The measurements were performed on one cobas e 411 analyzer, at one site, with one reagent lot, performing rackpack calibration according to instructions for use (every

7 days). PreciControls were run each day of the testing and met the target ranges. Repeatability and within-laboratory precision was calculated according to EP5-A2.

The calculated % CVs for the repeatability study (within-run precision) ranged from 2.3 to 3.6% for high negative serum, low positive serum, moderate positive serum and positive control (PC2). The SD (in s/co) for the negative serum and negative control (PC1) was 0.008 for both samples.

The calculated %CVs for the within-lab precision (also referred to as intermediate precision) ranged from 3.6 to 5.3% for the high negative serum, low positive serum, moderate positive serum and positive control (PC2). The SD (in s/co) for the negative serum and negative control (PC1), ranged from 0.011 – 0.049 for the negative serum and negative control (PC1). The results are shown below

1. Repeatability (within-run precision):

Sample	Mean (s/co)	SD (s/co)	CV (%)	n
Negative serum	0.104	0.008	8.0	80
High negative serum	0.968	0.034	3.6	80
Low positive serum	1.036	0.032	3.1	80
Positive serum	2.31	0.054	2.3	80
PC 1	0.133	0.008	5.9	80
PC 2	9.16	0.237	2.6	80

2. Within-Laboratory Precision:

Sample	Mean (s/co)	SD (s/co)	CV (%)	N
Negative serum	0.104	0.014	13.4	80
High negative serum	0.968	0.049	5.1	80
Low positive serum	1.036	0.045	4.3	80
Positive serum	2.31	0.084	3.6	80
PC 1	0.133	0.011	8.0	80
PC 2	9.16	0.484	5.3	80

PC 1-negative control
PC 2-positive control

J. Reproducibility

Precision was further evaluated incorporating between-run, between-day, between-lot and between-site variation. A reproducibility study was conducted following CLSI (Clinical Laboratory Standards Institute) EP5-A2 and CLSI EP15-A2 at three sites, on three different cobas e 411 analyzers-one at each site, using a total of three lots of reagents. Each site generated data on two lots of reagents. A five-member panel consisting of 3 serum pools (high negative, low positive and moderately positive) and 2 controls were assayed for 5 days in 2 runs per day at 3 replicates per run, for a total of 60 measurements for each panel member at each site. The analysis of data was

based on guidance from CLSI documents EP5-A2 and EP15-A2. Data were analyzed to determine SD and percent CV for within-run, between-run, between-day, between-lot, between-site and reproducibility. The overall imprecision data are summarized in the following table.

			Repeatability		Between Run		Between Day		Between Lot		Between Site		Reproducibility	
Sample	N	Mean COI[a]	SD[b]	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
High Negative Serum	180	0.942	0.017	1.8	0.024	2.6	0.026	2.8	0.033	3.4	0.000[c]	0.0	0.051	5.4
Low Positive Serum	180	1.161	0.019	1.7	0.026	2.2	0.030	2.6	0.036	3.1	0.019	1.7	0.060	5.2
Moderate Positive Serum	180	2.147	0.090	4.2	0.024	1.1	0.051	2.4	0.104	4.8	0.000[c]	0.0	0.148	6.9
PC 1	180	0.142	0.010	6.9	0.006	3.9	0.008	5.4	0.012	8.6	0.000[c]	0.0	0.018	12.9
PC 2	180	12.168	0.175	1.4	0.359	3.0	0.372	3.1	0.673	5.5	0.354	2.9	0.936	7.7

[a] COI - Cutoff index
[b] SD - Standard deviation
[c] SD of zero due to variance contributed by particular component was below stated significant figure.

K. 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, a 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								
	Reference anti-HCV		Elecsys® Anti-HCV		Chiron RIBA HCV 3.0 SIA			Difference in days to anti-HCV reactive Reference – Elecsys®[d]
Panel ID	Neg[e]	RX[f]	NR[g]	RX	Neg	Ind[h]	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

[d] 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.
[e] Neg = negative
[f] RX = reactive
[g] NR = non-reactive
[h] 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.

L. Genotype detection

Testing was performed to evaluate the ability of the Elecsys® Anti-HCV immunoassay on the cobas e 411 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 vendor: 1, 2, 3, 4, 5 and 6. The panels were tested with the Elecsys® Anti-HCV assay on the cobas e 411 analyzer and the comparator anti-HCV assay and final results were compared. The Elecsys® Anti-HCV assay on the cobas e 411 analyzer and the comparator anti-HCV assay results were in 100% agreement for the tested HCV genotypes.

M. 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. The study was performed by testing 341 samples from 31 potentially cross-reactive sub-groups. Of those, 279 samples were found to be non-reactive (negative) in both the Elecsys® Anti-HCV and the reference assay, 45 samples were found to be reactive in both assays, and 17 samples were found to be discordant between the Elecsys® Anti-HCV assay and the reference assay. The final results for each of the specimens were compared between the two assays. Specimen results that were discordant between the two assays were sent for supplemental RIBA testing.
The comparison of the analytical specificity between the two assays is 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[i]	RX[j]	NR	RX
Anti-nuclear antibody (ANA)	10	9	0	0	1
Cytomegalovirus (anti-CMV positive)	10	10	0	0	0
Dengue fever (*Flaviviridae* family)	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[k]	1
Elevated total protein	10	8	0	0	2
Epstein-Barr Virus (anti-EBV positive)	10	10	0	0	0
Escherichia coli (E. coli)	10	8	0	0	2
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[k]	0
Hepatitis D Virus (anti-HDV positive)	11	5	3[m]	0	3
Hepatitis E Virus (anti-HEV positive)	40	4	5[n]	1	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[l]	0	1
Influenza vaccine recipients	10	10	0	0	0
Multiparous female	10	10	0	0	0
Murray valley/Australian encephalitis (*Flaviviridae* family)	2	2	0	0	0
Non-viral liver disease	17	16	0	1[k]	0
Parvovirus B_{19} infection	10	8	1[o]	0	1
Rheumatoid Factor positive	10	9	0	0	1
Rubella	10	9	1[k]	0	0
Syphilis *(T. pallidum)*	10	9	0	1[k]	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[k]	0
Yeast infection	10	9	0	0	1
West Nile virus (*Flaviviridae* family)	11	11	0	0	0
Total	341	279	11	6	45

[i] NR = non-reactive
[j] RX = reactive
[k] RIBA testing resolved results in favor of Elecsys® assay.
[l] RIBA testing resolved results in favor of reference assay.
[m] 2 RIBA testing resolved results in favor of reference, 1 RIBA was indeterminate

[n)] 4 RIBA testing resolved results in favor of reference, 1 RIBA was indeterminate
[o)] RIBA testing was indeterminate.

Of the 17 discrepant results, RIBA favored the Elecsys® Anti-HCV assay in 41.2 % of the cases (7/17) and favored the reference assay in 41.2 % of the cases (7/17). In 17.6 % of the cases (3/17), the RIBA was indeterminate.

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 411 Immunoassay Analyzer. Clinical subjects were recruited prospectively based on clear description of inclusion and exclusion criteria from populations at risk for HCV infection. Two major prospective cohorts were selected based on risk and presence or absence of clinical and laboratory signs and symptoms of liver disease.

The study population included individuals with specific risks or history associated with HCV infection. The medical/clinical risks for HCV infection were: transfusions or transplants received before July 1992, clotting factors made before 1987 (hemophiliacs), known HIV infection, long-term hemodialysis, prenatal exposure (born to HCV-positive mothers), and a family history of any hepatitis condition. Occupational risks included healthcare workers, tattoo artists, morticians and individuals with history of incarceration. Sexual risks included individuals with multiple sex partners, individuals having sex with STD- diagnosed partner(s), men having sex with men, individuals having sex with HIV-infected partner(s) and commercial sex workers. Behavioral risks included IV drug use (current or past), sharing straw cocaine and individuals with tattoo or body piercing. Also included were individuals with signs or symptoms of liver disease (subjects must have had clinical symptoms or laboratory data or histological findings suggestive of hepatitis infection).

The signs and symptoms population included subjects that were hepatic (jaundice, discoloration of urine or stool), subjects with non-specific GI symptoms (nausea, vomiting), subjects with flu-like symptoms (fatigue, fever, joint pain), subjects with laboratory values (elevated ALT, AST, bilirubin) suggestive of liver disease, subjects with extrahepatic disease possibly associated with HCV (cryoglobulinemia, lymphoma, autoimmune thyroiditis, renal disease, dermatologic conditions such as lichen plannus and porphyria cutanea tarda), and subjects with histological findings suggestive of liver disease, if available. The signs and symptoms population also had to 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 these 2,206 subjects approximately 53% were enrolled in California, 40% in Florida, 2% in New Jersey and 5% in Georgia (New Jersey and Georgia started enrollment at a later date than the other sites). Samples obtained from 103 at risk and 7 symptomatic subjects were dropped due to predetermined subject discontinuation/exclusion criteria. Of the 2096 subjects that were available for testing and

analysis, 1,283 (61.2%) were from at risk subjects and 813 (38.8%) were from symptomatic subjects.

Of the 2,096 subjects, 609 (29.06%) were females and 1,487 (70.94%) were male. The mean age was 43 years, ranging from 21 to 81 years of age. Of the 1283 at risk subjects, 391 (30.48%) were females and 892 (69.52%) were males. The mean age was 42.6 years, ranging from 21 to 81 years of age. Of the 813 symptomatic subjects, 218 (26.81%) were females and 595 (73.19%) were males. The mean age was 43.5 years, ranging from 21 to 74 years of age.

Below is the demographic summary of the overall subject population by race/ethnicity.

Demographic summary of overall specimen population by race		
Race	Group	Percent
	N	%
African American / Black	1002	47.8
American Indian / Alaska Native	13	0.62
Asian	7	0.33
Caucasian / White	1054	50.3
Pacific Islander	5	0.24
Other	15	0.72
Total	2096	100

The clinical samples were assayed with one of the available lots of reagents on the cobas e 411 analyzer. The testing algorithm used to obtain anti-HCV result with the Elecsys assay was based on CDC recommendations and repeat testing, as defined in the labeling for the Elecsys assay, was included in the algorithm.

Approximately 61.2% (1283/2096) of the study subjects participating in the Elecsys® Anti-HCV clinical study reported no recent or current signs or symptoms of hepatitis.

A. Distribution of Results

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

Results for the Elecsys® Anti-HCV Assay in Study Subjects at Risk of HCV Infection

		Elecsys® Anti-HCV Result		
Age Group (Years)	Gender	Reactive n (%)	Non-Reactive n (%)	Total (n)
21 to 29	Female	1 (0.93)	107 (99.07)	108
	Male	3 (3.37)	86 (96.63)	89
30 to 39	Female	3 (3.49)	83 (96.51)	86
	Male	24 (13.26)	157 (86.74)	181
40 to 49	Female	25 (22.32)	87 (77.68)	112
	Male	74 (20.73)	283 (79.27)	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	10 (29.41)	24 (70.59)	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		267 (20.81)	1016 (79.19)	1283

The Elecsys anti-HCV assay on the cobas e411 analyzer was reactive in 267 (20.81%) of the individuals at risk for HCV.

The distribution of the Elecsys® Anti-HCV reactive and negative results among the study subjects with signs and symptoms of hepatitis stratified by age and gender are presented in the following table.

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

Age Group (Years)	Gender	Reactive		Non-Reactive		Total (n)
		N	%	N	%	
21 to 29	Female	4	8.00	46	92	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	88.3	94
40 to 49	Female	23	36.51	40	63.49	63
	Male	63	28.77	156	71.23	219
50 to 59	Female	14	31.11	31	68.89	45
	Male	95	55.56	76	44.44	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	3
	Male	0	0.00	1	100	1
80 to 89	Female	0	0.00	0	0.0	0
	Male	0	0.00	0	0.0	0
Total		239	29.40	574	70.6	813

The Elecsys anti-HCV assay on the cobas e 411 analyzer was reactive in 239 (29.40%) of the individuals with signs and symptoms of HCV infection.

B. Results by Specimen Classification

Following the testing with the reference anti-HCV assay and supplemental testing with the Chiron* RIBA* HCV 3.0 SIA, where indicated, 2096 subjects were assigned an Intermediate HCV status of HCV infected or not HCV infected based on the final results obtained with both assays as required.

Assignment of Intermediate HCV Status to the Study Population

Reference Anti-HCV Assay Result	Chiron* RIBA* HCV 3.0 SIA Result	Intermediate HCV Status
Negative	Not Applicable	Not HCV Infected
Reactive	Positive	HCV Infected: State or Associated Disease Not Determined
Reactive	Negative	Not HCV Infected
Reactive	Indeterminate	HCV Status Cannot be Determined (Not Determined)

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=2096). 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.

Hepatitis Rank Risk Group[p]	Intermediate HCV Status						Total
	HCV Infected		Not Determined		HCV Not Infected		
	Elecsys Anti-HCV Result		Elecsys Anti-HCV Result		Elecsys Anti-HCV Result		
	NR[q] (n)	RX[r] (n)	NR (n)	RX (n)	NR (n)	RX (n)	
Signs and Symptoms	1	213	2	14	571	12	813
Recipients of clotting factor	0	3	0	0	9	1	13
User of IV drugs (current or past)	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	558	5	646
Healthcare Worker	0	7	0	1	63	0	71
Other Lower Ranked[s]	0	36	1	1	259	3	300
Other Unranked[t]	0	1	0	0	5	1	7
Total	2	450	5	31	1583	25	2096

[p] Individuals at risk of HCV infection
[q] - Non-Reactive
[r] - Reactive
[s] - Individuals with risk factors ranked lower than top 6 risks.
[t] - Individuals with risk factors provided by subject that are not predefined in 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). 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 and the final HCV status of the 36 samples following supplemental PCR testing are presented in the following table.

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 RNA-NAT
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/Trans plant	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

The positive and negative percent agreements with 95% exact confidence interval between outcomes of the Elecsys Anti-HCV Assay on the cobas e 411 analyzer and the Final HCV Status based on interpretation of the reference assay with supplemental testing (RIBA and HCV-RNA) were calculated for different hepatitis ranked risk groups and symptomatic subjects, as presented below.

Elecsys Anti-HCV Results vs. the Final HCV Status

Hepatitis Ranked Risk Group[u]	Positive Percent Agreement	95% Exact Confidence Interval	Negative Percent Agreement	95% Exact Confidence Interval
Signs and Symptoms	99.55 (221/222)	97.52-99.99	96.95 (573/591)	95.23-98.19
Recipients of clotting factor	100.00 (3/3)	29.24-100.00	90.00 (9/10)	55.50-99.75
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	98.41 (558/567)	97.01-99.27
Healthcare Worker	100.00 (7/7)	59.04-100.00	98.44 (63/64)	91.60-99.96
Other Lower Rank[v]	100.00 (36/36)	90.26-100.00	98.48 (260/264)	96.17-99.59
Other Unranked[w]	100.00 (1/1)	2.50-100.00	83.33 (5/6)	35.88-99.58
Total	99.35 (461/464)	98.12-99.87	97.24 (1587/1632)	96.33-97.98

[u] - Individuals at risk of HCV infection
[v] - Individuals with risk factors ranked lower than top 6 risks.
[w] - Individuals with risk factors provided by subject that are not predefined in CRF.

The positive percent 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 negative percent 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 = 2096) base was 99.4% (461/464) 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 = 2096) was 97.2% (1587/1632) with a 95% confidence interval of 96.2% to 98.0%.

The positive percent agreement between the Elecsys Anti-HCV assay results and the 'HCV Infected' status for the symptomatic study population (n = 813) was 99.5% (221/222) with a 95% confidence interval of 97.5 - 100%. The negative percent

agreement between the Elecsys Anti-HCV assay results and the 'Not HCV Infected' status was 97.0% (573/591) with a 95% confidence interval of 95.2 - 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) with a 95% confidence interval of 97.1 - 99.9%. The negative percent agreement between the Elecsys Anti-HCV assay results and the 'Not HCV Infected' status was 97.4% 1014/1041) with a 95% confidence interval of 96.3 - 98.3%.

D. Potential Cross-reactivity with HBV Co-infected individuals

The samples in the study were tested with reference assays for HBsAg, HBsAg Confirmatory, and IgM anti-HAV to determine co-infection with HBV or HAV, respectively. All reference testing during the clinical laboratory study was performed following manufacturer's instructions using assays previously licensed or approved by the FDA. There were no HAV IgM positive samples identified. Among the samples tested for Hepatitis B surface antigen (HBsAg), 55 samples were identified as positive. The table below compares the Elecsys Anti-HCV assay results with HCV status according to the ranking of the risk of HCV infection in the HBsAg positive subjects.

Comparison of Elecsys Anti-HCV Results and HCV Status among HBsAg Positive Study Subjects (n = 55)					
Hepatitis ranked risk group	HCV status				Total
	HCV infected		Not HCV infected		
	Elecsys Anti-HCV assay result				
	NR	RX	NR	RX	
Signs and symptoms	0	5	11	0	16
IV drug user (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[x]	0	0	6	0	6
Other not ranked[y]	0	0	1	0	1
Total	0	12	38	5	55

[x)] Individuals with risk factors ranked lower than top 6 risks.
[y)] Individuals with risk factors provided by subject that are not predefined in CRF.

Of the 55 subjects infected with HBV, twelve had evidence of HCV-HBV co-infection. The positive percent agreement of the Elecsys Anti-HCV assay with the final HCV status in these patients was 100.00% (12/12); the negative percent

agreement for this group was 88.37% (38/43). Of the five patients with the positive HCV status which tested non-reactive in the Elecsys assay, four had RIBA indeterminate/RNA negative profiles, and one subject had negative RIBA results. An explanation for the RIBA indeterminate/RNA negative profiles are either past cleared infection representing long lasting residual antibody (to c22p and c33p) or non-specific false reactivity (to c33c and NS5). Early seroconversion also cannot be excluded. Finally, Roche demonstrated with a specificity study with 10 HBsAg positive samples that no cross-reactivity took place when 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.

B. Effectiveness Conclusions

Multicenter clinical studies were conducted in the US. The Elecsys Anti-HCV Immunoassay when used on cobas e 411 performed with clinical sensitivity and specificity comparable to current commercially available licensed assays.

- 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 99.55 (221/222) with a 95% confidence interval from 97.52% to 99.99%. The negative percent agreement with HCV final status for this group was 96.95% (573/591) with a 95% confidence interval of 95.23% to 98.19%.

- The comparison of the performance of the Elecsys Anti-HCV assay to the HCV status of the patients in the study, calculated for patients at risk of hepatitis C infection, resulted in a positive percent agreement of 98.34% (237/241) with a 95% confidence interval from 95.81% to 99.55%. The

negative percent agreement with the final HCV status for this group was 97.12% (1012/1042) with a 95% confidence interval of 95.92% to 98.05%.

- 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.

- 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.

- Analytical specificity studies evaluated the potential cross reactivity in specimens from individuals with medical conditions other than HCV infection. It has been shown that the device has no significant cross-reactivity with antibodies to other viral and bacterial pathogens 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.

- 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).

- Acceptable performance is obtained with the Elecsys Anti-HCV assay when testing specimens collected in serum or plasma (potassium EDTA, lithium heparin and sodium heparin).

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

XIII. CDRH DECISION

FDA issued an approval order on April 29, 2010.

The applicant's manufacturing facilities were inspected and found to be in compliance with the devices 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