Roche Diagnostics
Jamie Ferguson
Regulatory Affairs Principal
9115 Hague Road
Indianapolis, Indiana 46250

August 13, 2019

Re: K190428
Trade/Device Name: Elecsys Anti-HAV II
Regulation Number: 21 CFR 866.3310
Regulation Name: Hepatitis A Virus (HAV) Serological Assays
Regulatory Class: Class II
Product Code: LOL, QCH
Dated: February 20, 2019
Received: February 22, 2019

Dear Jamie Ferguson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

for

Maria Garcia, Ph.D.
Chief
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K190428

Device Name
Elecsys Anti-HAV II

Indications for Use *(Describe)*
Immunoassay for the in vitro qualitative detection of total antibodies (IgG and IgM) to hepatitis A virus (HAV) in human pediatric (ages 2 through 21 years) and adult serum and plasma (Li-heparin, potassium EDTA, Na-citrate, Na-heparin). The assay, in conjunction with other serological and clinical information, is indicated as an aid in the clinical laboratory diagnosis of acute or past hepatitis A virus infection in persons with signs or symptoms of hepatitis and in persons at increased risk for hepatitis A infection, or as an aid to identify HAV susceptible individuals and to determine the presence of an antibody response to HAV in vaccine recipients.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the cobas e immunoassay analyzers.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Elecsys Anti-HAV II
510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

In accordance with 21 CFR 807.87, Roche Diagnostics hereby submits official notification as required by Section 510(k) of the Federal Food, Drug and Cosmetics Act of our intention to market the device described in this Premarket Notification 510(k).

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA review and clearance for the Elecsys Anti-HAV II.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Jamie Ferguson Phone: (317) 521-4213 Fax: (317) 521-2324 Email: Jamie.ferguson@roche.com Tammy Dean Phone: (317) 521-3978 Fax: (317) 521-2324 Email: tammy.dean@roche.com
Date Prepared	February 20, 2019
Proprietary Name	Elecsys Anti-HAV II PreciControl Anti-HAV II
Common Name	Anti-HAV II PreciControl Anti-HAV II
Classification Name	1. Hepatitis A virus (HAV) Serological Assays 2. Assayed Quality Control Material for Clinical Microbiology Assays
Product Codes, Regulation Numbers	1. LOL, 21 CFR §866.3310 2. QCH, 21 CFR §866.3920, Quality Control
Predicate Devices	Elecsys Anti-HAV (K100903)
Establishment Registration	For the Elecsys Anti-HAV II, the establishment registration number for Roche Diagnostics GmbH in Mannheim, Germany is 9610126, and for Penzberg, Germany, 9610529. The establishment registration number for Roche Diagnostics in the United States is 1823260.

1. DEVICE DESCRIPTION

Elecsys Anti-HAV II is a second generation assay by Roche Diagnostics for the in vitro qualitative detection of total antibodies (IgG and IgM) to the hepatitis A virus (HAV) in human pediatric (ages 2 through 21 years) and adult serum and plasma. It is intended for use on the **cobas e** 601 immunoassay analyzer. The **cobas e** family of analyzers employs the electrochemiluminescence "ECLIA" technology. The assay is an 18-minute assay utilizing a competition principle.

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

The reagent rackpack working solutions include:

- M: Streptavidin-coated microparticles
- R1: HAV Ag (cell culture)
- R2: Biotinylated monoclonal anti-HAV antibody, monoclonal Anti-HAV antibody labeled with ruthenium complex
- AHAV 2 Cal1: Negative Calibrator 1 (human serum)
- AHAV 2 Cal2: Positive Calibrator 2 (anti-HAV (human), approximately 60 IU/L in human serum)

PreciControl Anti-HAV II is a ready-for-use control serum based on human serum both in the negative and positive concentration range. The controls are used for monitoring the performance of the Elecsys Anti-HAV II immunoassay. PreciControl Anti-HAV II is sold separately from the Elecsys Anti-HAV II immunoassay reagent.

2. INTENDED USE

Immunoassay for the in vitro qualitative detection of total antibodies (IgG and IgM) to hepatitis A virus (HAV) in human pediatric (ages 2 through 21 years) and adult serum and plasma (Li-Heparin, potassium EDTA, Na-Citrate, Na-Heparin). The assay, in conjunction with other

serological and clinical information, is indicated as an aid in the clinical laboratory diagnosis of acute or past hepatitis A virus infection in persons with signs or symptoms of hepatitis and in persons at increased risk for hepatitis A infection, or as an aid to identify HAV susceptible individuals and to determine the presence of an antibody response to HAV in vaccine recipients.

The **e**lectro**c**hemi**l**uminescence immunoassay "ECLIA" is intended for use on the **cobas e** immunoassay analyzers.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. This assay has not been FDA cleared or approved for the screening of blood or plasma donors.

3. TECHNOLOGICAL CHARACTERISTICS

Elecsys Anti-HAV II utilizes electrochemiluminescence "ECLIA" technology for the qualitative detection of total antibodies (IgG and IgM) to the hepatitis A virus (HAV) in human pediatric (ages 2 through 21 years) and adult serum and plasma on the **cobas e** 601 immunoassay analyzer.

The following tables compare the Elecsys Anti-HAV II with its predicate device, Elecsys Anti-HAV (K100903).

Table 1: Assay Comparison

Feature	Elecsys Anti-HAV (K100903)	Elecsys Anti-HAV II
Intended Use/Indications for Use	Immunoassay for the in vitro qualitative detection of total antibodies (IgM and IgG) to hepatitis A virus in human serum and plasma (K_2-EDTA). The assay is intended for use as an aid in the laboratory diagnosis of past or acute/recent hepatitis A infection. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection with hepatitis A virus in persons with signs or symptoms of hepatitis and in persons at risk for hepatitis A infection, or used as an aid to determine the presence of antibody response to HAV in vaccine recipients. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers. This assay is not intended for screening blood or solid or soft tissue donors. Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. The users are responsible for establishing their own assay performance characteristics in these populations.	Immunoassay for the in vitro qualitative detection of total antibodies (IgG and IgM) to hepatitis A virus (HAV) in human pediatric (ages 2 through 21 years) and adult serum and plasma (Li-Heparin, potassium EDTA, Na-Citrate, Na-Heparin). The assay, in conjunction with other serological and clinical information, is indicated as an aid in the clinical laboratory diagnosis of acute or past hepatitis A virus infection in persons with signs or symptoms of hepatitis and in persons at increased risk for hepatitis A infection, or as an aid to identify HAV susceptible individuals and to determine the presence of an antibody response to HAV in vaccine recipients. The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers. Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. This assay has not been FDA cleared or approved for the screening of blood or plasma donors.
Assay Method	Competition principle binding protein	Same
Detection Method	Electrochemiluminescence	Same
Applications/Test Time	18 minutes	Same
Instrument Platform	Elecsys 2010, **cobas e** 411, **cobas e** 601, **cobas e** 602, and MODULAR ANALYTICS E170	**cobas e** 601
Sample volume	50 µL	20 µL
Sample Type/Matrix	Human serum, plasma	Same
Sample Anticoagulants	K_2-EDTA	Li-Heparin, potassium EDTA, Na-Citrate, Na-Heparin
Calibrator	Anti-HAV Cal1 and Cal2 (packed in kit)	Anti-HAV II Cal1 and Cal2 (packed in kit)
Calibration Method	2-point calibration	Same

Feature	Elecsys Anti-HAV (K100903)	Elecsys Anti-HAV II
Calibration Interval	Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows: • after 1 month (28 days) when using the same reagent lot • after 7 days (when using the same reagent kit on the analyzer) • as required: e.g. quality control findings outside the defined limits	Same
Controls	PreciControl Anti-HAV	PreciControl Anti-HAV II
Traceability/Standardization	Second International Standard for Anti Hepatitis A, Immunoglobulin, Human, NIBSC code: 97/646	Same
Reagent Stability	Store at 2-8°C. Do not freeze. Store the Elecsys reagent kit upright in order to ensure complete availability of the microparticles during automatic mixing prior to use. Unopened at 2-8°C, up to stated expiration date. After opening at 2-8°C, 8 weeks. On the analyzers at 20-25°C, 7 days or 4 weeks when stored alternative in the refrigerator and on the analyzer, with the total time onboard on the analyzer not exceeding 40 hours.	Store at 2-8°C. Do not freeze. Store the Elecsys reagent kit upright in order to ensure complete availability of the microparticles during automatic mixing prior to use. Unopened at 2-8°C, up to stated expiration date. After opening at 2-8°C, 8 weeks. On the analyzers at 20-25°C, 8 weeks.

Feature	Elecsys Anti-HAV (K100903)	Elecsys Anti-HAV II
Limitations	Bilirubin < 855 µmol/L or < 50 mg/dL Hemolysis < 0.623 mmol/L or < 1.0 g/dL Lipemia < 1500 mg/dL Biotin < 205 nmol/L or < 50 ng/mL Criterion: Recovery within +/- 20% of initial value Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration. In vitro tests were performed on 18 commonly used pharmaceuticals (Acetylcystein, Ampicillin, Ascorbic acid, Ca Dobesilate, Cyclosporine, Cefoxitin, Heparin, Intralipid, Levodopa, Methyldopa, Metronidazole, Phenylbutazone, Tetracycline, Acetylsalicylic Acid, Rifampicin, Acetaminophen, Ibuprofen and Theophylline). No interference with the assay was found. In rare cases, interference due to extremely high titers of antibodies to analyte specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.	Bilirubin < 1129 µmol/L or ≤ 66 mg/dL Hemoglobin ≤ 0.621 mmol/L or ≤ 1000 mg/dL Intralipid ≤ 2000 mg/dL Rheumatoid Factors ≤ 1400 IU/mL IgG ≤ 7.0 g/dL IgA ≤ 1.6 g/dL IgM ≤ 1.0 g/dL Serum Albumin ≤ 7 g/dL Criterion: > 1.0 COI +/- 20% recovery, ≤ 1.0 COI +/- 0.20 recovery Negative specimens with biotin concentrations up to 100 ng/mL demonstrated ≤ 11 % negative bias in COI values. Biotin concentrations greater than 100 ng/mL lead to higher negative bias and in consequence can lead to false positive Elecsys Anti-HAV II results. Some studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after ingestion for subjects consuming supplements of 20 mg biotin per day and up to 1160 ng/mL in plasma for subjects consuming a single dose of 300 mg biotin. In vitro tests were performed on 18 commonly used pharmaceuticals (Acetylcystein, Ampicillin-Na, Ascorbic acid, Ca Dobesilate, Cyclosporine, Cefoxitin, Doxycycline, Heparin, Levodopa, Methyldopa +1.5, Metronidazole, Phenylbutazone, Tetracycline, Acetylsalicylic Acid, Rifampicin, Acetaminophen, Ibuprofen and Theophylline). No interference with the assay was found. In rare cases, interference due to extremely high titers of antibodies to analyte specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

4. NON-CLINICAL PERFORMANCE EVALUATION

Non-clinical performance evaluation for Elecsys Anti-HAV II is briefly summarized below.

4.1. Precision

4.1.1. Repeatability and Within-Laboratory Precision

Precision measurements were conducted to evaluate repeatability (within-run precision) and within-laboratory precision (intermediate precision) in a study based on the protocol of CLSI EP05-A3. Precision was evaluated on a single **cobas e** 601 immunoassay analyzer. One Elecsys Anti-HAV II reagent lot was evaluated. The protocol consisted of testing 2 aliquots each of two levels of control and 5 human sera per run, 2 runs per day for 21 days. Calibration was performed on day 1 and on day 17. Serum samples were human serum sample pools.

Table 2: Repeatability and Within-Laboratory Precision Results

		Repeatability		**Within-Laboratory (Intermediate) Precision**		
Sample	Mean (COI)	SD[a)] (COI)	CV (%)	SD (COI)	CV (%)	n
Human serum 1	1.42	0.016	1.1	0.028	2.0	84
Human serum 2	1.15	0.012	1.1	0.022	1.9	84
Human serum 3	0.955	0.009	0.9	0.022	2.3	84
Human serum 4	0.665	0.009	1.3	0.020	2.9	84
Human serum 5	0.006	0.0002	3.0	0.0002	3.3	84
PC[b)] Anti-HAV II 1	1.30	0.015	1.1	0.024	1.8	84
PC Anti-HAV II 2	0.339	0.005	1.5	0.009	2.7	84

a) SD = Standard Deviation

b) PC = PreciControl

4.2. Analytical Sensitivity

4.2.1. Determination of Cut-off Sensitivity

The cut-off of the Elecsys Anti-HAV II assay was established with internal studies, and the validation of the cut-off was performed by external clinical studies. In order to determine the cut-off sensitivity, the 2nd International Standard for Anti-Hepatitis A, Immunoglobulin, Human,

NIBSC code: 97/646 was serially diluted to 10 samples and tested fourfold with three different reagent and calibrator lots. The cut-off of COI = 1.0 corresponds to ≤ 25.4 IU/L.

Table 3: Lot MP01

Dilution-factor/ Sample	Target value [IU/L]	Measuring cell 1 [COI]		Measuring cell 2 [COI]		[COI]
		Run 1	Run 2	Run 1	Run 2	Mean
Ref-Std_01	0	1.31	1.28	1.31	1.30	1.30
Ref-Std_02	10.2	1.16	1.17	1.17	1.16	1.17
Ref-Std_03	20.3	1.05	1.03	1.06	1.04	1.05
Ref-Std_04	30.5	0.921	0.923	0.923	0.946	0.928
Ref-Std_05	59.9	0.628	0.626	0.637	0.646	0.634
Ref-Std_06	99.7	0.365	0.361	0.365	0.369	0.365
Ref-Std_07	200	0.098	0.098	0.104	0.102	0.100
Ref-Std_08	300	0.035	0.034	0.036	0.035	0.035
Ref-Std_09	400	0.017	0.017	0.017	0.017	0.017
Ref-Std_10	500	0.011	0.011	0.019	0.011	0.013
Cut-off sensitivity		24.6 IU/L				

Table 4: Lot PoQ

Dilution-factor/ Sample	Target value [IU/L]	Measuring cell 1 [COI]		Measuring cell 2 [COI]		[COI]
		Run 1	Run 2	Run 1	Run 2	Mean
Ref-Std_01	0	1.28	1.28	1.27	1.28	1.28
Ref-Std_02	10.2	1.14	1.15	1.17	1.17	1.16
Ref-Std_03	20.3	1.05	1.06	1.04	1.04	1.05
Ref-Std_04	30.5	0.941	0.944	0.934	0.942	0.940
Ref-Std_05	59.9	0.663	0.663	0.674	0.665	0.667
Ref-Std_06	99.7	0.389	0.399	0.399	0.401	0.397
Ref-Std_07	200	0.113	0.112	0.115	0.115	0.114
Ref-Std_08	300	0.039	0.038	0.040	0.040	0.040
Ref-Std_09	400	0.018	0.018	0.018	0.019	0.018
Ref-Std_10	500	0.011	0.011	0.011	0.011	0.011
Cut-off sensitivity		25.4 IU/L				

Table 5: Lot P02

Dilution-factor/ Sample	Target value [IU/L]	Measuring cell 1 [COI]		Measuring cell 2 [COI]		[COI]
		Run 1	Run 2	Run 1	Run 2	Mean
Ref-Std_01	0	1.25	1.25	1.26	1.27	1.26
Ref-Std_02	10.2	1.11	1.10	1.13	1.15	1.12
Ref-Std_03	20.3	0.976	0.975	0.982	0.984	0.980
Ref-Std_04	30.5	0.867	0.859	0.873	0.872	0.868
Ref-Std_05	59.9	0.551	0.548	0.563	0.559	0.555
Ref-Std_06	99.7	0.269	0.274	0.276	0.276	0.274
Ref-Std_07	200	0.048	0.048	0.049	0.048	0.048
Ref-Std_08	300	0.016	0.016	0.016	0.016	0.016
Ref-Std_09	400	0.010	0.010	0.010	0.010	0.010
Ref-Std_10	500	0.009	0.009	0.009	0.009	0.009
Cut-off sensitivity		20.1 IU/L				

4.3. Human Anti-Mouse Antibodies (HAMA)

The effect on detection of analyte in the presence of HAMA using the Elecsys Anti-HAV II was determined on the **cobas e** 601 immunoassay analyzer using 11 human serum samples. Only samples that are double positive for HAMA and anti-HAV antibodies were used, since HAMA interference would lead to false negative results in the competitive assay format. No HAMA interference was found within the predefined acceptance criteria.

4.4. Endogenous Interferences

4.4.1. Hemoglobin/Bilirubin/Lipemia

The purpose of this study was to evaluate endogenous substances for potential interference with the parameters measured on the Elecsys Anti-HAV II on the **cobas e** 601 immunoassay analyzer. For each interfering substance, four human serum samples were tested in accordance with CLSI EP07-A2.

4.4.2. Rheumatoid Factor Interference

The recovery of analyte values in the presence of endogenous interfering substances was determined with the Elecsys Anti-HAV II on the **cobas e** 601 immunoassay analyzer.

One aliquot of each serum sample was spiked with the interfering substance, and another aliquot with the same volume of the solvent (buffer matrix) of the interfering substance (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments.

The recovery for each sample was calculated by comparison to the reference sample.

4.4.3. Serum Albumin, IgG, IgA, and IgM Interference

One aliquot of each serum sample was spiked with the interfering substance (lyophilisate). In this case, another aliquot without any additives (since the interfering substance is a lyophilisate) was used as dilution pool. The interfering pool was then diluted into the dilution pool in 14.3% increments.

The deviation or recovery for each sample was calculated by comparison to the reference sample.

Conclusion:

All results met the pre-defined acceptance criteria, demonstrating no interference from endogenous substances up to the levels shown in the table below.

Table 6: Summary of Results – Endogenous Interfering Substances

Interferent	Interfering substance measured up to	No interference seen up to
Intralipid® (Lipemia)	2000 mg/dL	2000 mg/dL
Bilirubin	66 mg/dL	66 mg/dL
Hemoglobin	1000 mg/dL	1000 mg/dL
Rheumatoid Factor	2000 IU/mL	1400 IU/mL
human Serum albumin	7.00 g/dL	7.00 g/dL
human IgG	7.00 g/dL	7.00 g/dL
human IgM	1.00 g/dL	1.00 g/dL
human IgA	1.60 g/dL	1.60 g/dL

4.5. Biotin

The purpose of this study was to evaluate biotin for potential interference with the parameters measured on the Elecsys Anti-HAV II on the **cobas e** 601 immunoassay analyzer. Five human serum samples were tested in accordance with CLSI EP07-A2. Negative specimens with biotin

concentrations up to 100 ng/mL demonstrated ≤11% negative bias in COI values. Biotin concentrations greater than 100 ng/mL lead to higher negative bias and in consequence can lead to false positive Elecsys Anti-HAV II results. Refer to Limitations for additional information on biotin interference.

4.6. Analytical Specificity/Cross-Reactivity

The effect on detection of analyte in the presence of potential cross-reacting antibodies using the Elecsys Anti-HAV II was determined on the **cobas e** 601 immunoassay analyzer with native human serum and plasma sample pools.

Anti-HAV negative samples containing potential cross-reacting antibodies to other infectious diseases were measured with Elecsys Anti-HAV and Elecsys Anti-HAV II. In total, 10 samples with acute Hepatitis B infection, 10 samples with acute Hepatitis C infection, 10 samples with HIV infection, 10 samples with EBV infection, 10 samples with Anti-CMV antibodies, 10 samples with Anti-HSV antibodies, 10 samples with Toxoplasma Gondii infection, 10 samples with Treponema Pallidum infection, 10 samples with Anti-Mumps/Rubeola antibodies, 10 samples with Anti-Rubella antibodies, 10 samples with Anti-Parvovirus B19 antibodies and 10 samples with ANA Autoimmune antibodies were tested.

No cross-reactivity with other infectious agents was found.

4.7. Exogenous Interferences – Drugs

The recovery of analyte values in the presence of drugs was determined by comparing values obtained from samples spiked with 18 commonly used pharmaceutical compounds (Acetylcystein, Ampicillin-Na, Ascorbic acid, Ca-Dobesilate, Cyclosporine, Cefoxitin, Doxycycline, Heparin, Levodopa, Methyldopa +1.5, Metronidazole, Phenylbutazone, Tetracycline, Acetylsalicylic Acid, Rifampicin, Acetaminophen, Ibuprofen and Theophylline) with the reference sample (unspiked). Four human serum samples (native human serum pools) were used and tested on the **cobas e** 601 immunoassay analyzer according to CLSI EP07-A2. The drug concentrations tested correspond at least to the five times maximum daily doses. The four serum samples were divided into aliquots and spiked with the potential interferents. The reference sample without interferent was spiked with the respective amount of solvent only.

The Elecsys Anti-HAV II concentration (as COI) of the spiked aliquots was determined in three-fold determination and compared to the Elecsys Anti-HAV II result determined for the reference aliquot (also in three-fold determination) on one **cobas e** 601 immunoassay analyzer.

All results met the pre-defined acceptance criteria, demonstrating no interference from the drug substances at the tested concentrations.

4.8. Sample Matrix Comparison

The recovery of analyte values in the presence of anticoagulants with the Elecsys Anti-HAV II was determined on the **cobas e** 601 immunoassay analyzer by comparing Elecsys Anti-HAV II results obtained from samples drawn into serum and plasma collection tubes. The samples were spiked with anti-HAV positive samples from individual donors to obtain a range of anti-HAV concentrations. The recovery of each plasma sample to the matching serum sample was calculated. At least 60 serum/plasma pairs were tested for each kind of anticoagulant in single determination (K_2-EDTA, K_3-EDTA, Na-Heparin, Li-Heparin, Na-Citrate).

The specifications were met for all anti-coagulants, demonstrating that K_2-EDTA, K_3-EDTA, Na-Heparin, Li-Heparin, and Na-Citrate are acceptable sample types for use with Elecsys Anti-HAV II.

4.9. Analytical Method Comparison to Predicate

A method comparison of Elecsys Anti-HAV II on the **cobas e** 601 immunoassay analyzer versus the predicate device, Elecsys Anti-HAV, was conducted according to CLSI EP09-A3.

A total of 215 modified serum samples (≥100 negative and ≥100 positive samples) were measured in singleton on **cobas e** 601 immunoassay analyzer. The samples were primarily prepared by mixing negative and positive sera from individual donors.

Results for the method comparison between Elecsys Anti-HAV II and Elecsys Anti-HAV met the pre-defined acceptance criteria, which demonstrates equivalency between the candidate and predicate devices.

Table 7: Analytical Method Comparison Agreement Rates Between Elecsys Anti-HAV II and Elecsys Anti-HAV

Elecsys Anti-HAV II Result	Elecsys Anti-HAV Result		
	Reactive	**Borderline**	**Non-Reactive**
Reactive	107	2	0
Non-Reactive	0	8	98
Total	**107**	**10**	**98**

The positive percent agreement rate was 100% (107/107), the negative percent agreement rate was 100% (98/98). Of ten samples with results in the borderline zone of the predicate device, Elecsys Anti-HAV, 20% (2/10) were positive and 80% (8/10) were negative by the Elecsys Anti-HAV II.

4.10. Reagent Stability

The reagent stability testing was performed in two different studies:

- Study 1: Reagent stability after first opening at 2-8°C (8 weeks)
- Study 2: On-board reagent stability (8 weeks)

4.10.1. Reagent Stability After First Opening

Elecsys Anti-HAV II reagent kits can be used after first opening for up to 8 weeks when stored at 2-8°C. Reagent stability after first opening for the Elecsys Anti-HAV II assay was tested on one **cobas e** 601 immunoassay analyzer.

A fresh reagent rackpack was placed on the analyzer and calibrated. Reference values for the samples tested were determined. After initial measurement the kit was removed from the analyzer and kept at 2-8 °C for 35 and 63 days. After 35 and 63 days, the kit was placed on the analyzer again, calibrated, and the test samples were determined. Recovery was calculated based on the result at time-point Day 0. Two control samples and seven samples were tested in duplicate.

All pre-defined acceptance criteria were met, demonstrating reagent stability for 8 weeks after first opening at 2-8°C.

4.10.2. On-Board Reagent Stability

Elecsys Anti-HAV II reagent kits can be stored on-board the analyzers for up to 8 weeks. A new calibration of the kit kept on-board is recommended every 7 days.

Reagent on-board stability for the Elecsys Anti-HAV II assay was tested on one **cobas e** 601 immunoassay analyzer. A fresh reagent rackpack was placed on the analyzer and calibrated. All samples were measured on day 0. On day 22, 29, 35, 49 and 63, the same samples were measured with the same reagent kit kept at 20°C ± 3°C (on-board condition) using the calibration curves established on day 0, 22, 29, 35, 49 and 63, respectively. Recovery was calculated based on the result at time-point Day 0. Two control samples were tested in singleton and seven samples were tested in duplicate.

All pre-defined acceptance criteria were met, demonstrating reagent on-board stability for 8 weeks on the **cobas e** 601 immunoassay analyzer.

4.11. Calibration Stability

To test calibration stability, two studies were completed, including:

- Study 1: Lot calibration stability
- Study 2: On-board calibration stability

4.11.1. Lot Calibration Stability

Calibration of an Elecsys Anti-HAV II reagent lot is recommended every 28 days (4 weeks). During that time period, fresh reagent kits of the same lot can be used without calibration using the calibration curve of the Day 0 reagent kit.

Elecsys Anti-HAV II was calibrated with a fresh reagent kit on day 0 using a **cobas e** 601 immunoassay analyzer. After 35 days (5 weeks), a new reagent kit of the same lot was used and recovery of samples was determined using the calibration curve of Day 0. Two control samples were tested in singleton and seven human serum samples were tested in duplicate.

All pre-defined acceptance criteria were met, demonstrating renewed calibration is recommended after 4 weeks when using the same reagent lot.

4.11.2. On-Board Calibration Stability

On-board calibration stability for the Elecsys Anti-HAV II assay was tested on one **cobas e** 601 immunoassay analyzer. A fresh reagent rackpack was placed on the analyzer and calibrated. All samples were measured on day 0. On day 8, the same samples were measured with the same reagent kit kept at 20°C ± 3°C (on-board condition) using the calibration curves established on day 1. Two control samples were tested in singleton and seven human serum samples were tested in duplicate.

All pre-defined acceptance criteria were met, demonstrating that a calibration can be used for up to one week when using the same lot of reagents stored on the analyzer.

4.12. Sample Stability

To test sample stability, four studies were completed, including:

- Study 1: Sample stability at 2-8°C
- Study 2: Sample stability at room temperature (15-25°C)
- Study 3: Sample stability at -15 to -25°C
- Study 4: Freeze/thaw cycles

4.12.1. Sample Stability at 2-8°C

Six human serum, K_2-EDTA, Li-Heparin, and Na-Citrate plasma samples and seven K_3-EDTA and Na-Heparin plasma samples were aliquoted and measured fresh (reference value) and after storage at 2-8°C for 14 days. Measurements were performed with three-fold determination on a **cobas e** 601 immunoassay analyzer and recovery was calculated as percent of the reference value.

All pre-defined acceptance criteria were met, demonstrating the specimens are stable for 14 days at 2-8°C.

4.12.2. Sample Stability at Room Temperature (15-25°C)

Six human serum, K_2-EDTA, Li-Heparin, and Na-Citrate plasma samples and seven K_3-EDTA and Na-Heparin plasma samples were aliquoted and measured fresh (reference value) and after

storage at 15-25°C for 6 days. Measurements were performed with three-fold determination on a **cobas e** 601 immunoassay analyzer and recovery was calculated as percent of the reference value.

All pre-defined acceptance criteria were met, demonstrating the specimens are stable for 6 days at 15-25°C.

4.12.3. Sample Stability at -15 to -25°C

Six human serum, K_2-EDTA, Li-Heparin, and Na-Citrate plasma samples and seven K_3-EDTA and Na-Heparin plasma samples were aliquoted and measured fresh (reference value) and after storage at -15 to -25°C for 3 months. Measurements were performed with three-fold determination on a **cobas e** 601 immunoassay analyzer and recovery was calculated as percent of the reference value.

All pre-defined acceptance criteria were met, demonstrating the specimens are stable for 3 months at -15 to -25°C.

4.12.4. Sample Stability – Freeze/Thaw Cycles

Six human serum, K_2-EDTA, Li-Heparin, and Na-Citrate plasma samples and seven K_3-EDTA and Na-Heparin plasma samples were aliquoted and measured fresh (reference value) and after five freeze/ thaw cycles. Measurements were performed with three-fold determination on a **cobas e** 601 immunoassay analyzer and recovery was calculated as percent of the reference value.

All pre-defined acceptance criteria were met, demonstrating the specimens are stable for 5 freeze/thaw cycles.

5. EXTERNAL (CLINICAL) TESTING

5.1. Reproducibility

Precision results were collected on three different **cobas e** 601 immunoassay analyzers across three external testing sites utilizing a single lot of Elecsys Anti-HAV II reagent. Four human serum pools and two Elecsys Anti-HAV II PreciControl materials were tested in three replicates

per run, two runs per day for a 5-day format according to CLSI EP05-A3. All testing was performed on the same analyzer with a new rackpack for each day. Repeatability, within-laboratory, and reproducibility were calculated as SD and CV values.

Ten dummy specimens were tested in each run, as well as between runs, so as to separate the runs within each day. The data were evaluated by Component of Variance Analysis.

Table 8: Results - Elecsys Anti-HAV II and PreciControls Anti-HAV II on cobas e 601 Immunoassay Analyzer (all sites combined)

						Repeatability		Between Run		Between Day		Between Site		Reproducibility	
Specimen Material	**N**	**Mean**	**Median**	**Min**	**Max**	**SD (95% CI)**	**% CV (95% CI)**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD (95% CI)**	**% CV (95% CI)**
HSP 01	90	0.813	0.814	0.764	0.856	0.010 (0.012)	1.3 (1.5)	0.016	1.9	0.000	0.0	0.011	1.3	0.022 (0.031)	2.7 (3.8)
HSP 02	90	0.904	0.908	0.846	0.953	0.012 (0.014)	1.3 (1.5)	0.016	1.8	0.000	0.0	0.014	1.5	0.024 (0.036)	2.7 (4.0)
HSP 03	90	1.009	1.010	0.934	1.070	0.018 (0.021)	1.7 (2.1)	0.013	1.3	0.004	0.4	0.016	1.6	0.027 (0.041)	2.7 (4.1)
HSP 04	90	0.449	0.450	0.408	0.478	0.005 (0.006)	1.1 (1.3)	0.011	2.5	0.000	0.0	0.007	1.5	0.014 (0.020)	3.1 (4.4)
PC A-HAV2_L1	90	1.299	1.300	1.230	1.350	0.018 (0.022)	1.4 (1.7)	0.009	0.7	0.010	0.7	0.018	1.4	0.029 (0.046)	2.2 (3.5)
PC A-HAV2_L2	90	0.376	0.375	0.347	0.410	0.006 (0.007)	1.6 (1.9)	0.013	3.3	0.000	0.0	0.003	0.9	0.014 (0.018)	3.8 (4.8)

One-sided upper 95% confidence interval displayed

5.2. Method Comparison Versus Predicate

The Elecsys Anti-HAV II was performed at each of the three clinical laboratories with a single lot of reagent to assess the performance of the assay in a testing environment that most closely resembles that of the final user. The objective of this study was to provide data for US- and non-US-obtained specimens by testing the Elecsys Anti-HAV II on the **cobas e** 601 immunoassay analyzer and comparing the results to an FDA-cleared predicate assay. The Elecsys Anti-HAV assay was used as the predicate device for comparison at each of the three laboratories. The study included specimens from patients in the following cohorts: routine HAV testing, hospitalized, increased risk, symptomatic, characterized acute HAV infected, and pediatric.

Table 9: Method Comparison Results (all sites combined)

	Elecsys Anti-HAV Assay Results (all sites combined)			
Elecsys Anti-HAV II Results	Reactive ≥ 22 IU/L	Border 18.0 ≤ IU/L < 22.0	Non-Reactive < 18.0 IU/L	Total
Reactive COI ≤ 1.0	501	6	16	523
Non-Reactive COI >1.0	0	1	437	438
Total	501	7	453	961

	Absolute	**Relative %**	**95 % CI**
PPA[c)]	501/502	99.80	98.90; 99.99
NPA[d)]	437/459	95.21	92.83; 96.97

c) PPA = Positive Percent Agreement

d) NPA = Negative Percent Agreement

Positive percent agreement and negative percent agreement with their respective 95th percentile confidence interval (CI) for each cohort are summarized in the following table. The lower end of the 95% confidence intervals for PPA ranged from 90.45% in the hospitalized cohort to 97.18% in the symptomatic cohort. The lower end of the ≥ 95% confidence intervals for NPA ranged from 52.36% in the pediatric cohort to 93.04% in the hospitalized cohort. For the pediatric cohort, there were 14 specimens negative by both the predicate Elecsys Anti-HAV assay and the Elecsys Anti-HAV II assay. There were 4 discordant results, of which 2 were borderline with the predicate assay but positive with the Elecsys Anti-HAV II assay and 2 were negative with the predicate assay but positive with the Elecsys Anti-HAV II assay. Discordant results were counted against Elecsys Anti-HAV II when calculating agreement (77.8%). The lower bound of the 95% CI for the NPA in the pediatric population is influenced by the small number of specimens (n = 18). The overall percentages for all cohorts combined met the expected performance of a lower bound of the 95% confidence interval of ≥ 90% for the agreement rates (positive and negative) versus the predicate assay (Elecsys Anti-HAV assay). The lower limit of the confidence interval for the PPA was 98.90%, and the lower limit of the confidence interval for NPA was 92.83%.

Table 10: Percent Agreements for the Various Specimen Cohorts

Summary of the percent agreements for various specimen cohorts: Elecsys Anti-HAV II[e] assay versus the predicate (Elecsys Anti-HAV assay)[f]				
Cohort	PPA		NPA	
	PPA (x/n)	95 % CI	NPA (x/n)	95 % CI
Routine HAV testing	100 (91/91)	(96.03, 100)	94.50 (103/109)	(88.40, 97.95)
Hospitalized	98.21 (55/56)	(90.45, 99.95)	97.22 (140/144)	(93.04, 99.24)
Increased risk for hepatitis	100 (119/119)	(96.95, 100)	94.25 (82/87)	(87.10, 98.11)
Symptomatic	100 (129/129)	(97.18, 100)	96.70 (88/91)	(90.67, 99.31)
Characterized acute HAV	100 (65/65)	(94.48, 100)	100 (10/10)	(69.15, 100)
Pediatric	100 (42/42)	(91.59, 100)	77.78 (14/18)	(52.36, 93.59)
Overall	99.80 (501/502)	(98.90, 99.99)	95.21 (437/459)	(92.83, 96.97)

e) Cutoff of 1.0 COI used for Elecsys Anti-HAV II assay

f) Specimens with results in the borderline range of (18.0 ≤ IU/L < 22.0) for Elecsys Anti-HAV assay were counted as discordant with the Elecsys Anti-HAV II assay

5.3. Pre- and Post-HAV Vaccination

Specimens from 49 subjects that were collected both pre- and post-HAV vaccination were evaluated by the Elecsys Anti-HAV II assay and the predicate assay (Elecsys Anti-HAV). The post-vaccination specimens were obtained at least 4 weeks, but not more than 10 weeks, after the completion of the vaccine regimen. Three HAV vaccines, which are currently licensed in the U.S., were used. No discrepant results were observed.

5.4. Prevalence Study

The Elecsys Anti-HAV II assay was used to evaluate the prevalence of HAV antibodies in an apparently healthy population (presumed normal, healthy individuals without symptoms derived by a self-reporting health questionnaire). A statistically significant number of subjects were collected in a presumed “high prevalence” region, the Western United States, and a presumed

"low prevalence" region, the Eastern United States. Testing based on the predicate assay was not required.

The collection site representing the Eastern US recruited 431 subjects. Of the 431 subject, 31 were classified as screen failures and therefore did not complete the informed consent process. A total of 400 subjects satisfied the inclusion/exclusion criteria and proved acceptable specimens for analysis. The collection site representing the Western US recruited 427 subjects. Of the 427 subjects, 24 were classified as screen failures and therefore did not complete the informed consent process. An additional three subjects were dropped from enrollment. A subject was allowed to be dropped from enrollment if defined conditions were met after the screening process was completed and the informed consent process was successfully completed. Both collection sites were open to the recruitment/enrollment of subjects for Prevalence cohort only. Each site was instructed to collect 400 evaluable specimens, which was accomplished.

The results were consistent with a higher prevalence of reactive HAV results reported in the Western US, 53.75%, versus the Eastern US 29.50%.

6. ADDITIONAL INFORMATION

The Elecsys Anti-HAV II is intended to be used with the following calibrators and controls:

- PreciControl Anti-HAV II
- Anti-HAV II Cal1 and Anti-HAV II Cal2, which is included in the kit

7. CONCLUSIONS

The information provided in this 510(k) Premarket Notification supports a determination of substantial equivalence for the Elecsys Anti-HAV II. The data from the non-clinical and clinical tests demonstrate that the device is as safe, as effective, and performs as well as the predicate device.