510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number: K093955

B. Purpose for Submission: Clearance of New Device

C. Measurand: IgM Antibody to *Hepatitis A Virus* in serum and *heparinized* plasma

D. Type of Test: Electrochemiluminescence immunoassay (ECLIA)

E. Applicant: Roche Diagnostics

F. Proprietary and Established Names: Elecsys Anti-HAV IgM immunoassay
Elecsys PreciControl Anti-HAV IgM

G. Regulatory Information:

1. Regulation section: 21 CFR §866.3310, Hepatitis A virus Serological Assays
   21 CFR §862.1660, Quality Control Material
2. Classification: Class II
3. Product code: LOL (Hepatitis A Test - IgM Antibody)
   JJX (Quality control material, assayed and unassayed)
4. Panel: Microbiology (83)

H. Intended Use:

1. Intended use(s):

   The Roche Elecsys Anti-HAV IgM immunoassay is used for the in vitro qualitative detection of IgM antibodies to hepatitis A virus (anti-HAV IgM) in human serum and plasma (potassium EDTA, lithium or sodium heparin, sodium citrate). The assay is intended for use as an aid in the laboratory diagnosis of an acute or recently acquired hepatitis A virus 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 and symptoms of hepatitis and in persons at risk for hepatitis A infection.
   The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Elecsys PreciControl Anti-HAV IgM is used for quality control of the Elecsys Anti-HAV IgM immunoassay on the 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 user is responsible for establishing their own assay performance characteristics in these populations.

Caution: U.S. Federal Law restricts this device to sale by or on the order of a physician.

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Elecsys 2010 and cobas e 411 analyzers; MODULAR ANALYTICS E170 and cobas e 601 analyzers

I. Device Description:

The Roche Elecsys Anti-HAV IgM immunoassay is the electrochemi-luminescence immunoassay "ECLIA" intended for use on Elecsys and cobas e immunoassay analyzers. Samples are pretreated with anti-Fdγ reagent to block specific IgG in the presence of monoclonal anti-HAV antibodies labeled with ruthenium complex. After addition of biotinylated monoclonal h-IgM-specific antibodies, HAV antigen, and streptavidin-coated microparticles in the second incubation step, the anti-HAV IgM antibodies present in the sample form a sandwich complex with the HAV antigen and the ruthenium-labeled anti-HAV antibody which becomes bound to the solid phase via interaction of biotin and streptavidine. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode, and unbound substances are then removed with ProCell. Voltage application to the electrode induces chemiluminescent emission, which is then measured by a photomultiplier. Results are determined automatically by the Elecsys and cobas e software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by anti-HAV IgM calibration.

J. Substantial Equivalence Information:

1. Predicate device name(s): Abbott AxSym HAV AB-M 2.0

2. Predicate Numbers (s): P790019/S011

3. Comparison with predicate:

Similarities

Anti-HAV IgM Immunoassay Comparison		
Feature	**Elecsys Anti-HAV IgM Assay**	**Predicate Device Abbott Axsym HAVAB-M 2.0 Assay**
Intended Use	Immunoassay for the in vitro qualitative detection of IgM antibodies to hepatitis A virus in human serum and plasma (lithium heparin and potassium EDTA). The assay is intended for use as aid in the laboratory diagnosis of an acute or recently acquired 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. The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.	Immunoassay for the qualitative detection of IgM antibody to hepatitis A virus (IgM anti-HAV) in human serum or plasma (potassium EDTA, sodium heparin, sodium citrate, or lithium heparin). A test for IgM anti-HAV is indicated as an aid in the laboratory diagnosis of acute or recent hepatitis A viral 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 fro hepatitis A infection.
Indications for Use	Same	Same
Sample Type	Human serum and plasma	Same

Differences

Anti-HAV IgM Immunoassay Comparison		
Features	**Elecsys Anti-HAV IgM Assay**	**Predicate Device Abbott Axsym HAVAB-M 2.0 Assay**
Detection Protocol	**E**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay (ECLIA)	Microparticle Enzyme Immunoassay (MEIA)

Traceability/ Standardization	Roche Internal Standard	Not Given
Interpretation of Results	≥1.10 Reactive ≥ 0.90 - < 1.10 Grayzone <0.9 Negative	>1.20 Reactive 0.80 -1.20 Grayzone <0.80 Nonreactive
Calibration Interval	Once per reagent lot and • 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 specified limits	A single sample of both the Negative and Positive Controls must be tested as a means of evaluating the assay calibration. Once the calibration is accepted and stored, all subsequent samples may be tested without further calibration unless one or more of the following occur: • A reagent pack with a new lot number is used • Either of the AxSYM HAVAB-M 2.0 Control values is out of its specified range • The MEIA Optics Verification Update has been performed
Controls	Elecsys PreciControl Anti-HAV IgM	Abbott AxSYM HAVAB-M 2.0 Controls

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP5-A2, "Evaluation of Precision Performance of Quantitative Measurement Methods"
CLSI EP17-A, "Protocols for Determination of Limits of Detection"
Class II Special Controls Guidance Document: Hepatitis A Virus Serological Assays: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071055.pdf

L. Test Principle:

The Elecsys Anti-HAV IgM immunoassay utilizes a μ-capture test concept based on a monoclonal h-IgM directed biotinylated antibody, cell culture derived Hepatitis A Virus and a ruthenylated monoclonal antibody directed to HAV. Capture of formed immune complexes from the reaction mixture is based on biotin binding to streptavidin-coated magnetic microparticles which are collected on a measuring cell electrode. Signal generation is triggered by the application of a voltage to the electrode (electrochemiluminescence technology). The level of signal count detected by the system increases as the concentration of the IgM antibody target present in a patient sample increases.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision and Reproducibility was determined using Elecsys reagents, human sera, and controls. Precision studies were performed at one internal site on the Elecsys 2010 and cobas e 411 and Modular Analytics E170 and cobas e 601 analyzers using a single lot of reagents. PreciControls AHAVIGM 1 and 2 (PC1 and PC2) materials and three human serum pools (high negative HSP3, low positive HSP1 and moderately positive HSP2) were tested in replicates of 2 in 2 runs/day for 20 days for intermediate and repeatability precision according to the CLSI EP15-A2/EP5-A2. Precision results are presented below.

Reproducibility was performed at three external sites on three different Elecsys 2010 as well as on three Modular Analytics E170 analyzers. Three human serum pools (high negative HSP3, low positive HSP1 and moderately positive HSP2) were tested in replicates of 3 in 2 runs/day for 5 days according to the CLSI EP15-A2/EP5-A2.

Precision on Elecsys 2010

		Repeatability[1]		**Intermediate Precision[2]**	
Sample	**Mean**	**SD**	**CV**	**SD**	**CV**
	COI	COI	%	COI	%
HS pool 1	1.14	0.03	2.6	0.051	4.5
HS pool 2	2.23	0.06	2.7	0.094	4.2
HS pool 3	0.884	0.018	2.1	0.035	4
PC A-HAVIGM1	0.23	0.004	1.5	0.009	4.1
PC A-HAVIGM2	2.04	0.05	2.5	0.098	4.8

1) Repeatability = within-run precision

2) Intermediate precision = between-run and between-day variation

Precision on MODULAR ANALYTICS E170

		Repeatability[1]		Intermediate Precision[2]	
Sample	Mean	SD	CV	SD	CV
	COI	COI	%	COI	%
HS pool 1	1.22	0.024	2	0.06	4.9
HS pool 2	2.36	0.052	2.2	0.11	4.7
HS pool 3	0.929	0.018	1.9	0.04	4.4
PC A-HAVIGM1	0.217	0.005	2.3	0.01	4.5
PC A-HAVIGM2	2.13	0.043	2	0.11	5.1

1) Repeatability = within-run precision

2) Intermediate precision = between-run and between-day variation

Reproducibility on the Elecsys 2010

	Mean		Repeatability[1]		Intermediate precision[2]		Between-day		Between-site		Reproducibility (total)	
Sample	COI[3]	N	SD[4]	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
HSP1	0.917	90	0.031	3.4	0.007	0.8	0.003	0.3	0.023	2.5	0.039	4.3
HSP2	1.12	90	0.034	3	0.024	2.1	0.0	0	0.025	2.2	0.048	4.3
HSP3	2.24	90	0.086	3.8	0.05	2.2	0.0	0	0.029	1.3	0.104	4.6
PC A-HAVIGM1	0.239	90	0.006	2.6	0.00	0.0	0.004	1.9	0.01	4.4	0.013	5.4
PC A-HAVIGM2	1.65	90	0.049	3	0.021	1.3	0.058	3.5	0.027	1.6	0.083	5.1

1) Repeatability = within-run precision
2) Intermediate precision = between run and between day
3 COI = cutoff index
4) SD = standard deviation

Reproducibility on the MODULAR ANALYTICS E170												
	Mean		Repeatability[1]		Intermediate precision[2]		Between-day		Between-site		Reproducibility (total)	
Sample	COI[3]	N	SD[4]	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
HSP1	0.923	90	0.019	2.1	0.02	2.1	0.000[5]	0	0.014	1.5	0.031	3.4
HSP2	1.13	90	0.026	2.3	0.024	2.1	0.000[5]	0	0.000[5]	0.0	0.035	3.1
HSP3	2.30	90	0.046	2.0	0.078	3.4	0.000[5]	0	0.000[5]	0.0	0.091	4.0
PC A-HAVIGM1	0.213	90	0.004	1.9	0.000[5]	0.0	0.001	0.4	0.016	7.7	0.017	8.0
PC A-HAVIGM2	1.67	90	0.048	2.9	0.047	2.8	0.000	0.0	0.018	1.1	0.069	4.2

1) Repeatability = within-run precision
2 Intermediate precision = between run and between day
3 COI = cutoff index
4) SD = standard deviation
5) SD of zero due to variance contributed by particular component was below stated significant figure.

b. Linearity/assay reportable range:
N/A

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability: This method has been standardized against a Roche standard. The units have been selected arbitrarily.

Stability:

Reagents:

unopened at 2-8 °C	up to the stated expiration date
M, R1, R2 after opening at 2-8 °C	8 weeks
on MODULAR ANALYTICS E170 and cobas e 601	8 weeks
on Elecsys 2010 and cobas e 411	8 weeks
Cal1, Cal2 after opening at 2-8 °C	8 weeks
on Elecsys 2010 and cobas e 411 at 20-25 °C	up to 5 hours
on MODULAR ANALYTICS E170 and cobas e 601	use only once

Controls:

unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on the analyzers at 20-25 °C	up to 14 hours

Samples:
Sample stability was determined using different sample materials e.g., Serum, Serum with separating gel, K_2-EDTA,- Li-Heparin,- Na-Heparin and Na-Citrate Plasma. Three negative, three low positive, and one positive samples were tested and compared with fresh reference materials. The potential influence of different frozen human samples after storage at -20°C for 3 months was evaluated and showed satisfactory recovery. Similarly, studies of 5 freeze thaw cycles, sample stability for 7 days at 2-8°C, and sample stability at 25°C for 2 hours resulted in satisfactory recovery within the specified acceptance criteria.

d. Detection limits:

Limit of detection (LoD) of the Elecsys® Anti-HAV IgM assay was determined according to CLSI EP17-A. The LoD was determined as the lowest amount of analyte in a sample that can be detected with 95% probability. The distribution of values for five low-level human serum samples has been determined on two Elecsys® 2010 Analyzers over 3 days, 2 runs per day. Samples were measured in one-fold determination in each run. In summary, 30 measuring points were collected per instrument.

$LOD = LOB + 1.6529 \times SD_{total}$ (of low analyte samples)
LOD was determined to be 0.268 COI, and is reported in the labeling as 0.4 COI.

Limit of Blank (LoB) of the Elecsys® Anti-HAV IgM assay was determined according to CLSI EP17-A. Limit of Blank determines the highest observed measurement values for samples free of analyte. The LoB was determined as the 95th percentile of measurements of blank samples. The distribution of values for five zero-level human serum and plasma samples has been determined on two Elecsys® 2010 Analyzers over 3 days, 2 runs per day. The LoB claim in the package insert will be set to 0.3 COI.

Calibrators: Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (Cal1): 100 - 2000 (Elecsys 2010, MODULAR ANALYTICS E170 and cobas e analyzers).
Positive calibrator (Cal2): 5000 - 30000 (Elecsys 2010, MODULAR ANALYTICS E170 and cobas e analyzers).

e. Analytical specificity:

Cross-reactivity: The Elecsys anti-HAV IgM assay on the Elecsys 2010 was used to test 211 samples from 15 potentially cross-reactive sub-groups. Samples (n = 209) were found to be nonreactive (negative) in both the Elecsys anti-HAV IgM and the predicate assays, and no samples were found to be reactive in both assays and 2 samples were found to be discordant between the Elecsys anti-HAV IgM and the AxSym assays. The testing results are summarized in the table below:

Cross-reactant	**No. tested**	**Elecsys Anti-HAV IgM/ Reference Neg/Neg**	**Elecsys Anti-HAV IgM/ Reference Equivocal/ Neg**	**Elecsys Anti-HAV IgM/ Reference Neg/ Equivocal**	**Elecsys Anti-HAV IgM/ Reference Pos/Pos**
ANA	11	10	0	1[a]	0
CMV	13	13	0	0	0
EBV	16	16	0	0	0
Elevated IgG	13	13	0	0	0
Elevated IgM	12	11	1[b]	0	0
HBV	20	20	0	0	0
HCV	11	11	0	0	0
HIV	11	11	0	0	0
HSV	11	11	0	0	0
Mumps/ Rubella	15	15	0	0	0
Parvo B19	15	15	0	0	0
Rheumatoid factor	12	12	0	0	0
Rubella	20	20	0	0	0
Toxoplasmosis	16	16	0	0	0
VZV	15	15	0	0	0
Total	**211**	**209**	**1**	**1**	**0**

[a] Elecsys 2010 Negative/AxSym Equivocal
[b] Elecsys 2010 Equivocal/AxSym Negative

Human anti-mouse antibodies (HAMA) effect was tested by comparing the recovery of 10 human serum samples spiked with HAMA versus 10 unspiked aliquots of samples. No HAMA effect was found.

Interference: The impact of endogenous interfering substances on the Elecsys Anti-HAV IgM assay was determined testing native human serum pools on

Elecsys® 2010 Immunoassay Analyzer.

The assay is unaffected by icterus (bilirubin < 855 µmol/L or < 50 mg/dL), hemolysis (Hb < 0.623 mmol/L or < 1.0 g/dL), lipemia (Intralipid < 2000 mg/dL), and biotin < 205 nmol/L or < 50 ng/mL. Serum pools (high negative, low positive, and high positive) were used to spike with the intereferent. One aliquot of each serum sample was spiked with the interfering substance, another aliquot was spiked with the same volume of isotonic NaCl solution (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments. The % recovery (COI) was determined by dividing the mean value of the measured concentration by the expected concentration. Criterion: Recovery of positive samples within ± 20 % of initial value. In patients receiving therapy with high biotin doses (i.e. > 5 mg/day), no sample should be taken until at least 8 hours after the last biotin administration.

In vitro tests were performed on 18 commonly used pharmaceuticals (Acetylcysteine, Ampicillin-Na, Ascorbic acid, Ca-Dobesilate, Ciclosporine, Cefoxitin, Heparin, Intralipid, Levodopa, Methyldopa, Metronidazole, Phenylbutazone, Doxycycline, Acetylsalicylic acid, Rifampicin, Acetaminophen, Ibuprofen, and Theophylline) and in addition on folic acid. No interference with the assay was found.

f. *Assay cut-off:* The cutoff for the Elecsys anti-HAV IgM assay was initially established by measuring a total of 1004 samples including 575 negative from post acute, dialysis, hospitalized**,** routine samples with request for anti-HAV-IgM testing, samples from blood donors and 429 positive samples from seroconverters < 90 days (commercial sources), HAV follow ups after infection < 90 days and samples suspected for HAV- obtained from several European sites. The distribution of positive, equivocal and negative results was compared with the predicate assay AxSym HAV AB M-2.0 and the cutoffs were set as noted below. The result of a sample is given in the form of a cutoff index (signal sample/cutoff). Results obtained with the Elecsys Rubella IgM assay can be interpreted as follows:

Non-reactive: ≥ 0.90 COI; Border: ≥ 0.90 - < 1.10 COI; Reactive: ≥ 1.0 COI

Samples with a COI < 0.90 are considered non-reactive in the Elecsys Anti-HAV IgM assay and no further testing is necessary. Samples with a COI ≥ 1.10 are considered reactive in the Elecsys Anti-HAV IgM assay. Samples with a COI between 0.90 and < 1.10 are considered border (borderline). The sample should be retested in duplicate.

- If 2 of the 3 results have a COI < 0.90, the result is interpreted as non-reactive and no further testing is necessary.

- If 2 of the 3 results have a COI between 0.90 and < 1.10, the result is interpreted as borderline. It is recommended that a specimen be drawn in two weeks and retested.
- If 2 of the 3 results have a COI ≥ 1.10, the result is interpreted as reactive.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of Cal1 and Cal2.

2. Comparison studies:

a. Method comparison with predicate device:
The performance of the Elecsys anti-HAV IgM assay was determined by percent agreement among negative samples and percent agreement among positive samples, against a consensus comparator method, in specific populations. The main predicate (Abbott AxSym HAV AB-M 2.0) was used as sole comparator/reference.

b. Matrix comparison:
The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys® Anti-HAV IgM Immunoassay was determined on Elecsys® 2010 Immunoassay Analyzer by comparing values obtained from native samples (single donors) drawn into Serum, Li- and Na-Heparin Plasma, Citrate- and K_2-EDTA plasma and Serum-gel primary tubes. Reference for all sample types was serum drawn into Serum primary tubes (without Gel).
Acceptance criterion for single pairs are:
• Samples ≤ 0.5 COI: recovery ± 0.3 COI
• Samples > 0.5 COI: recovery 80-120 %

The following tables summarize the results for the comparison between serum and 4 plasma matrices.

Plasma matrix	**Number of positive specimens showing recovery to serum within various ranges**		
	< 10 %	10 - 15 %	> 15 %
Li-heparin	9	1	0
Na-heparin	9	1	0
K_2-EDTA	10	0	0
Sodium citrate	9	1	0

Plasma matrix	**Number of borderline specimens showing recovery to serum within various ranges**

	< 10 %	10 - 15 %	> 15 %
Li-heparin	15	0	0
Na-heparin	15	0	0
K_2-EDTA	15	0	0
Sodium citrate	12	3	0

Plasma matrix	**Number of negative specimens showing recovery to serum within various ranges**		
	< 0.1 COI	0.1 - 0.3 COI	> 0.3 COI
Li-heparin	20	0	0
Na-heparin	20	0	0
K_2-EDTA	20	0	0
Sodium citrate	20	0	0

3. Clinical studies:

   a. Clinical Sensitivity: N/A

   b. Clinical specificity: N/A

   c. *Other clinical supportive data* (when a. and b. are not applicable):

Clinical Performance

Clinical Study Cohorts:

A multi-center study was conducted in the U.S. to characterize the performance of the Elecsys Anti-HAV IgM immunoassay. All subjects were tested with the Elecsys Anti-HAV IgM assay on the Elecsys 2010 analyzer and with an FDA-cleared reference method in strict accordance with the manufacturer's package insert instructions.
A total of 1087 samples were obtained from multiple specimen sources, representing subjects for whom routine hepatitis A testing had been ordered, hospitalized patients, subjects at increased risk for hepatitis, subjects with signs and symptoms of hepatitis, subjects characterized with acute hepatitis A, and subjects below the age of 21 years (pediatric/adolescents). All samples (prospective and retrospective) are stored frozen before shipment to Roche and to the respective sites for testing.

The positive percent agreement and the negative percent agreement results for

the different clinical population are presented in the following table:

Percent Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Symptomatic Individuals (Prospective)

anti-HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1			**Site 2**			**Site 3**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	0	0	1	0	0	0	0	0	0	0	0	1
Equivocal	0	0	0	0	0	0	0	0	0	0	0	0
Negative	0	0	172	0	0	0	0	0	39	0	0	211
Total	0	0	173	0	0	0	0	0	39	0	0	212
PPA	0.00 (0/0)			0.00 (0/0)			0.00 (0/0)			0.00 (0/0)		
95% CI	0.00 to 100.00			0.00 to 100.00			0.00 to 100.00			0.00 to 100.00		
NPA	99.42 (172/173)			0.00 (0/0)			100.00 (39/39)			99.53 (211/212)		
95% CI	96.82 to 99.99			0.00 to 100.00			90.97 to 100.00			97.40 to 99.99		

Percent Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Specimens Subjected to Routine Hepatitis A Testing (Prospective)

anti-HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1			**Site 2**			**Site 3**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	0	2	0	0	0	0	1	0	0	1	2	0
Equivocal	0	0	0	0	0	0	0	0	0	0	0	0
Negative	0	1	148	0	0	0	0	0	59	0	1	207
Total	0	3	148	0	0	0	1	0	59	1	3	207
PPA	0.00 (0/1)			0.00 (0/0)			100.00 (1/1)			50.00 (1/2)		
95% CI	0.00 to 97.50			0.00 to 100.00			2.50 to 100.00			1.26 to 98.74		
NPA	98.67 (148/150)			0.00 (0/0)			100.00 (59/59)			99.04 (207/209)		
95% CI	95.27 to 99.84			0.00 to 100.00			93.94 to 100.00			96.59 to 99.88		

Percent Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Hospitalized Patients (Prospective)

anti-HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1			**Site 2**			**Site 3**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	0	0	0	0	0	0	0	0	0	0	0	0
Equivocal	0	0	0	0	0	0	0	0	0	0	0	0
Negative	0	0	134	0	0	0	0	0	82	0	0	216
Total	0	0	134	0	0	0	0	0	82	0	0	216
PPA	0.00 (0/0)			0.00 (0/0)			0.00 (0/0)			0.00 (0/0)		
95% CI	0.00 to 100.00			0.00 to 100.00			0.00 to 100.00			0.00 to 100.00		
NPA	100.00 (134/134)			0.00 (0/0)			100.00 (82/82)			100.00 (216/216)		
95% CI	97.28 to 100.00			0.00 to 100.00			95.60 to 100.00			98.31 to 100.00		

Percent Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Subjects Characterized as Acute Hepatitis A (Prospective)

anti--HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1			**Site 2**			**Site 3**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	35	0	3	0	0	0	0	0	0	35	0	3
Equivocal	1	0	0	0	0	0	0	0	0	1	0	0
Negative	0	0	6	0	0	0	0	0	0	0	0	6
Total	36	0	9	0	0	0	0	0	0	36	0	9
PPA	97.22 (35/36)			0.00 (0/0)			0.00 (0/0)			97.22 (35/36)		
95% CI	85.47 to 99.93			0.00 to 100.00			0.00 to 100.00			85.47 to 99.93		
NPA	66.67 (6/9)			0.00 (0/0)			0.00 (0/0)			66.67 (6/9)		
95% CI	29.93 to 92.51			0.00 to 100.00			0.00 to 100.00			29.93 to 92.51		

Percent Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Subjects Characterized as Acute Hepatitis A (Retrospective)

anti-HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1 BW			**Site 2 WU**			**Site 3 JH**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	36	0	0	0	0	0	46	1	0	82	1	0
Equivocal	0	0	0	0	0	0	1 [c]	0	0	1 [c]	0	0
Negative	0	0	3	0	0	0	0	0	2	0	0	5
Total	36	0	0	0	0	0	47	1	2	83	1	5
PPA	100.00 (36/36)			0.00 (0/0)			97.87 (46/47)			98.80 (82/83)		
95% CI	90.26 to 100.00			0.00 to 100.00			88.71 to 99.95			93.47 to 99.97		
NPA	100.00 (3/3)			0.00 (0/0)			66.67 (2/3)			83.33 (5/6)		

Percent Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Pediatric and Adolescent Subjects (Retrospective)

anti-HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1			**Site 2**			**Site 3**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	0	0	0	0	0	0	0	0	0	0	0	0
Equivocal	0	0	0	0	0	0	0	0	0	0	0	0
Negative	0	0	3	0	0	0	0	0	96	0	0	99
Total	0	0	3	0	0	0	0	0	96	0	0	99
PPA	0.00 (0/0)			0.00 (0/0)			0.00 (0/0)			0.00 (0/0)		
95% CI	0.00 to 100.00			0.00 to 100.00			0.00 to 100.00			0.00 to 100.00		
NPA	100.00 (3/3)			0.00 (0/0)			100.00 (96/96)			100.00 (99/99)		
95% CI	29.24 to 100.00			0.00 to 100.00			96.23 to 100.00			96.34 to 100.00		

Agreement for Elecsys and Predicate anti-HAV IgM Assay Results from Subjects at Increased Risk for Hepatitis (Retrospective)

anti-HAV IgM Assay Results												
Elecsys Result	**Predicate Result**											
	Site 1			**Site 2**			**Site 3**			**All Sites**		
	RX	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**	**RX**	**EQ**	**NR**
Reactive	0	0	0	0	0	0	0	0	0	0	0	0
Equivocal	0	0	0	0	0	0	0	0	0	0	0	0
Negative	0	0	17	0	0	0	0	0	198	0	0	215
Total	0	0	17	0	0	0	0	0	198	0	0	215
PPA	0.00 (0/0)			0.00 (0/0)			0.00 (0/0)			0.00 (0/0)		
95% CI	0.00 to 100.00			0.00 to 100.00			0.00 to 100.00			0.00 to 100.00		
NPA	100.00 (17/17)			0.00 (0/0)			100.00 (198/198)			100.00 (215/215)		
95% CI	80.49 to 100.00			0.00 to 100.00			98.15 to 100.00			98.30 to 100.00		

Summary of the Percent Agreements for the Various Specimen Cohorts

	Positive Percent agreement		**Negative percent agreement**	
Cohort	PPA (x/n)	95 % confidence interval	NPA (x/n)	95 % confidence interval
Overall	97.5 (118/121)	92.9 - 99.5	99.3 (959/966)	98.5 - 99.7
Routine HAV testing	50.0 (1/2)	1.26 - 98.7	99.0 (207/209)	96.6 - 99.9
Hospitalized	0.00 (0/0)	0.00 - 100	100 (216/216)	98.3 - 100
Signs and symptoms	0.00 (0/0)	0.00 - 100	99.5 (211/212)	97.4 - 99.99
High risk for hepatitis	0.00 (0/0)	0.00 - 100	100 (215/215)	98.3 - 100
Characterized acute HAV	98.3 (117/119)	94.1 - 99.8	73.3 (11/15)	44.9 - 92.2
Pediatric/ adolescent	0.00 (0/0)	0.00 - 100	100 (99/99)	96.3 - 100

Note: Additional testing was performed for the discrepant and several concordant specimens with a second FDA cleared anti-HAV IgM assay. The second predicate agreed with the Elecsys outcome in 7 of the 10 discrepant samples and with the first predicate in 2 of the 10 specimens. Remaining one specimen, reactive by the test device and nonreactive with first predicate, was

equivocal with second predicate. Complete concordance was obtained among the three assays in the fifteen non-reactive and reactive concordant specimens that were also tested.

Prevalence Studies:

The Elecsys Anti-HAV IgM assay was used to evaluate the prevalence of HAV IgM antibodies in an apparently healthy population (normal, healthy individuals without symptoms). The prospective study population for the Elecsys Anti-HAV IgM assay consisted of 602 patients. Of these 602 patients, 300 patients were from the high prevalence region, Western states of the U.S. (New Mexico) and 302 patients were from the low risk region Eastern states of the U.S. (Indiana). The prospective study population was 208 (34.6 %) males and 394 (65.4 %) females (total n = 602) including 493 (81.9 %) Caucasian + 32 (5.3 %) African American + 6 (1.0 %) Asian + 69 (11.5 %) American Indian + 2 (0.3 %). The results of prevalence population are summarized according to age groups in decades, gender, geographical area and the number of reactive, non-reactive and equivocal results.

Expected results for the Elecsys Anti-HAV IgM assay in subjects from low prevalence areas for Hepatitis A

Age range	Gender	Elecsys Anti-HAV IgM results						Total
		Reactive		Equivocal		Non-reactive		
		N	Percent	N	Percent	N	Percent	
11 - 20	Female	0	0	0	0	1	100	1
	Male	0	0	0	0	1	100	1
21 - 30	Female	0	0	0	0	7	100	7
	Male	0	0	0	0	6	100	6
31 - 40	Female	0	0	0	0	21	100	21
	Male	0	0	0	0	2	100	2
41 - 50	Female	0	0	0	0	22	100	22
	Male	0	0	0	0	13	100	13
51 - 60	Female	0	0	0	0	42	100	42
	Male	0	0	0	0	19	100	19
61 - 70	Female	0	0	0	0	51	100	51
	Male	0	0	0	0	28	100	28
71 - 80	Female	0	0	0	0	48	100	48
	Male	0	0	0	0	30	100	30
> 80	Female	0	0	0	0	5	100	5
	Male	0	0	0	0	6	100	6
All ages	Female	0	0	0	0	197	100	197
	Male	0	0	0	0	105	100	105
Total		0	0	0	0	302	100	302

Prevalence rate for reactive anti-HAV IgM antibody in specimens collected in a low prevalence region, Eastern states of the US (Indiana), was 0.00 %.

Expected results for the Elecsys Anti-HAV IgM assay in subjects from high prevalence areas for Hepatitis A								
Age range	Gender	Elecsys Anti-HAV IgM results						Total
		Reactive		Equivocal		Non-reactive		
		N	Percent	N	Percent	N	Percent	
11- 20	Female	0	0	0	0	8	100	8
	Male	0	0	0	0	5	100	5
21 - 30	Female	0	0	0	0	17	100	17
	Male	0	0	0	0	11	100	11
31 - 40	Female	0	0	0	0	27	100	27
	Male	0	0	0	0	13	100	13
41 - 50	Female	0	0	0	0	52	100	52
	Male	0	0	0	0	18	100	18
51 - 60	Female	0	0	0	0	54	100	54
	Male	0	0	0	0	24	100	24
61 - 70	Female	0	0	0	0	25	100	25
	Male	1	4	0	0	24	96	25
71 - 80	Female	0	0	0	0	12	100	12
	Male	0	0	0	0	7	100	7
> 80	Female	0	0	0	0	1	100	1
	Male	0	0	0	0	0	0	0
un-known	Female	0	0	0	0	1	100	1
	Male	0	0	0	0	0	0	0
All ages	Female	0	0	0	0	197	100	197
	Male	1	0.97	0	0	102	99	103
Total		1	0.33	0	0	299	99.7	300

Prevalence rate for reactive anti-HAV IgM antibody in specimens collected in a high prevalence region, Western states of the US (New Mexico), was 0.33 %.

HAV Vaccination:

Fifty-four non-HAV-vaccinated, anti-HAV total non-reactive subjects were immunized with three Hepatitis A vaccines approved for use in the United States. Vaccine was randomly assigned to subjects as they enrolled: 20 for HAVRIX, 18 for TWINRIX and 16 for VAQTA. Two vaccination studies are represented: one conducted in the Eastern region of the US and the other in Penzberg Germany. Concordant assay results were obtained with all pre- and post-vaccination specimens. There was no IgM response observed in post-

vaccination specimens with the exception of two specimens which were equivocal/borderline and just reactive (repeat testing generated equivocal/ borderline results), respectively.

Seroconversion Sensitivity:

Seroconversion sensitivity of the Elecsys anti-HAV IgM assay was shown by testing 3 seroconversion panels in comparison to that of the comparator assay (Abbott AxSym HAV AB-M 2.0). Seroconversion panel results were also compared with the data provided by the vendor for the Abbott HAV AB-M 2.0 assay. The results are summarized in the following table:

Elecsys anti-HAV IgM assay Seroconversion Panel Results

Panel ID	Elecsys 2010 assay		Comparator anti-HAV IgM assay[1]		Comparator anti-HAV IgM assay[2]	
	Post bleed day of earliest reactive result	Post bleed day of last positive result	Post bleed day of earliest reactive result	Post bleed day of last positive result	Post bleed day of earliest reactive result	Post bleed day of last positive result
HAV-01	0	21	0	34	0	28
[3]PHT 902	16	21	Not tested	Not tested	16	21
RP013	9	162	51	85	51	85

[1]The comparator results were shown by Roche using the Abbott AxSym HAV AB-M 2.0.

[2]The comparator results were provided by Vendor using the Abbott HAV AB-M.

[3]The panel was not tested with the reference assay (AxSym HAV AB-M 2.0) due to the limited sample volume.

Method Comparison studies on two instruments:

The method comparison for the Elecsys anti-HAV IgM assay between the two platforms E2010 and E170 was demonstrated by testing the prevalence and other clinical cohort specimens on three external MODULAR Analytics E170 and cobas e 601modules and three external Elecsys 2010 and cobas e 411 analyzers. There were a total of 602 specimens from the Prevalence cohort and 1084 specimens from the clinical cohorts which had evaluable results from both instruments. The samples were distributed across the six analyzers such that each sample was analyzed on one E170 and one E2010. The regression analyses for the comparisons using the prevalence cohort and the combined clinical cohorts were carried out using the least squares and Passing-Bablok regression methods.

Prevalence: The Pearson's regression correlation for the 602 data pairs from the Prevalence cohort was 0.9935. The Positive percent agreement was 1/1 = 100.0 (95% Exact confidence limits of 2.50 to 100.0). The Negative percent agreement

was 601/601 = 100.0 (95% Exact confidence limits of 99.39 to 100.0).

Clinical Cohort: The Pearson's regression correlation for the 1084 data pairs from the non-prevalence clinical cohorts was 0.9925. Positive percent agreement was 123/126 = 97.62 (95% Exact confidence limits of 93.20 to 99.51). Negative percent agreement was 957/958 = 99.90 (95% Exact confidence limits of 99.42 to 100.0).

4. Clinical cut-off**:**

   Refer to assay cutoff section above for the additional details. There are no Internationally Standards for anti-HAV IgM.

5. Expected values/Reference range:

   The Elecsys anti-HAV IgM assay was used to evaluate the prevalence of HAV IgM antibodies in an apparently healthy population (normal, healthy individuals without symptoms). A statistically significant number of subjects were prospectively collected in a "high prevalence" region, the Western states, and a "low prevalence" region, the Eastern states and were tested using only the Elecsys anti-HAV IgM assay and were not compared with the predicate device. Expected Results from low and high Prevalence based on the test device are presented under the prevalence study section. Prevalence rate for reactive anti-HAV IgM antibody in specimens collected in a high prevalence region, Western states of the US (New Mexico), was 0.33 %. Prevalence rate for reactive anti-HAV IgM antibody in specimens collected in a low prevalence region, Eastern states of the US (Indiana), was 0.00 %.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.