510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K203227

B Applicant

Roche Diagnostics

C Proprietary and Established Names

Elecsys HCG STAT

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DHA	Class II	21 CFR 862.1155 - Human Chorionic Gonadotropin (HCG) Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared assay (k002148) to decrease interference to biotin.

B Measurand:

Human Chorionic Gonadotropin (hCG)

C Type of Test:

Quantitative immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
For the in vitro quantitative determination of human chorionic gonadotropin (hCG) in human serum and plasma. The Elecsys HCG STAT immunoassay is intended for use in the early detection of pregnancy.

C Special Conditions for Use Statement(s):
For Prescription Use Only

D Special Instrument Requirements:
Cobas e 601 immunoassay analyzer.

IV Device/System Characteristics:

A Device Description:
The Elecsys HCG STAT is an immunoassay that uses antibodies labeled with ruthenium complex consist of a chimeric construct from human and mouse specific components.
The reagent working solutions include:
Rack Pack (kit placed on the analyzer).

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-hCG-Ab~biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-hCG antibody (mouse) 2.3 mg/L; phosphate buffer 40 mmol/L, pH 7.5; preservative.
- R2 Anti-hCG-Ab~Ru(bpy)23+ (black cap), 1 bottle, 10 mL:Monoclonal anti-hCG antibody (mouse) labeled with ruthenium complex 6.0 mg/L; phosphate buffer 40 mmol/L, pH 6.5; preservative.

B Principle of Operation:
The Elecsys HCG STAT immunoassay uses sandwich test principle using monoclonal antibodies specifically directed against Human Chorionic Gonadotropin (HCG). During a 9-minute incubation, hCG present in the sample reacts with biotinylated monoclonal hCG-specific antibody and streptavidin-coated microparticles to form a sandwich immune complex, which is bound to the solid phase. The reaction mixture is aspirated into a measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed. Application of a voltage to the electrode induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve.

V *Substantial Equivalence Information:*

A Predicate Device Name(s):
Elecsys HCG Test System

B Predicate 510(k) Number(s):
K002148

C Comparison with Predicate(s):

Device & Predicate Device(s):	K203227	K002148
Device Trade Name	Elecsys HCG STAT	Elecsys HCG Test System
General Device Characteristic Similarities		
Intended Use/Indications For Use	Immunoassay for the in vitro quantitative determination of human chorionic gonadotropin in human serum and plasma. Elecsys HCG STAT is intended for use especially in the diagnosis and monitoring of pregnancy.	Same
Assay Method	Electrochemiluminescence immunoassay	Same
Sample type	Serum and Plasma (Lithium heparin, K2-EDTA, and K3-EDTA)	Same
Test time	9 minutes	Same
General Device Characteristic Differences		
Measuring range	1.0-10,000 mIU/mL	0.500-10,000 mIU/mL
Biotin Interference	This assay is unaffected by biotin concentrations up to 3600 ng/mL	This assay is unaffected by biotin concentrations up to 40 ng/mL

VI Standards/Guidance Documents Referenced:

Clinical and Laboratory Standards Institute (CLSI) EP05-A3 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Third Edition.

CLSI EP06-A Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.

CLSI EP07 Interference Testing in Clinical Chemistry; Approved Guideline —Third Edition.

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   The sponsor provided three (3) precision studies: a 21-day precision study, a 5-day precision study and a multiple-site precision study. Please see below for details.

21 Day Precision Study

Precision was evaluated on one cobas e 601 analyzer according to CLSI guideline EP05-A3. The protocol consisted of testing two replicates of each control (PC1-PC2) and human serum samples (HS1-HS5) per run, in two runs per day for 21 days with one reagent lot. The results of the study are shown below.

21-Day Precision									
Sample	**Mean hCG conc. (mIU/mL)**	**Repeatability**		**Between Run**		**Between Day**		**Intermediate precision**	
		SD	**CV%**	**SD**	**CV%**	**SD**	**CV%**	**SD**	**CV %**
HS1	5.01	0.117	2.3	0.0673	1.3	0.272	5.4	0.304	6.1
HS2	8.38	0.211	2.5	0.010	0.1	0.419	5.0	0.469	5.6
HS3	3211	38.3	1.2	61.9	1.9	93.2	2.9	118	3.7
HS4	6305	89.1	1.4	83.5	1.3	291	4.6	315	5.0
HS5	9691	139	1.4	181	1.9	232	2.4	325	3.4
PC1	5.50	0.105	1.9	0.093	1.7	0.110	2.0	0.178	3.2
PC2	47.3	1.31	2.8	0.412	0.9	0.875	1.8	1.63	3.4

5 Day Precision Study

Precision was evaluated on one cobas e 601 analyzer according to CLSI guideline EP05-A3. The protocol consisted of testing 5 replicates of each control (PC1-PC2) and human serum samples (HS1-HS5) per run, one run per day for five days with three reagent lots. The results of from a representative lot are shown below.

5-Day Precision							
Sample	**Mean hCG conc. (mIU/mL)**	**Repeatability**		**Between Day**		**Intermediate precision**	
		SD	**CV%**	**SD**	**CV%**	**SD**	**CV %**
HS1	4.05	0.034	0.8	0.058	1.4	0.067	1.7
HS2	5.04	0.082	1.6	0.074	1.5	0.111	2.2
HS3	3434	43.0	1.3	36.7	1.1	56.5	1.6
HS4	5664	114	2.0	0.000	0.0	114	2.0
HS5	9591	150	1.6	77.5	0.8	169	1.8
PC1	5.66	0.123	2.2	0.069	1.2	0.141	2.5
PC2	46.0	0.761	1.7	0.411	0.9	0.865	1.9

Multiple Sites (Reproducibility) Study

The Reproducibility study was performed for a total of one run per day with five replicates of each human serum sample (HSP 1-6) and each control (CTR 1-2) per run, one run per day. The study was performed in two external laboratories and one internal laboratory. The samples were run in randomized order on the analyzers. Human serum pools (HSP 1-4) and diluted single donor samples (HSP 5-6) were used to calculate Repeatability and Intermediate precision according to CLSI EP05-A3. The results of the study are shown below.

Sample Material	Mean [mIU/mL]	Repeatability (Within-run Precision)		Intermediate Precision	
		SD [mIU/mL]	CV [%]	SD [mIU/mL]	CV [%]
Site 1					
HSP1	4.25	0.103	2.4	0.120	2.8
HSP2	7.30	0.129	1.8	0.165	2.3
HSP3	2969	44.9	1.5	44.9	1.5
HSP4	5783	63.2	1.1	77.8	1.3
HSP5	9093	127	1.4	132	1.5
HSP6	9303	147	1.6	149	1.6
CTR1	4.82	0.0912	1.9	0.105	2.2
CTR2	43.8	0.558	1.3	0.820	1.9
Site 2					
HSP1	4.84	0.0865	1.8	0.126	2.6
HSP2	7.98	0.137	1.7	0.157	2.0
HSP3	3030	30.1	1.0	51.2	1.7
HSP4	5895	62.1	1.1	70.5	1.2
HSP5	9242	156	1.7	170	1.8
HSP6	9501	108	1.1	111	1.2
CTR1	5.41	0.106	2.0	0.1228	2.3
CTR2	45.4	0.415	0.9	0.5668	1.2
Site 3					
HSP1	4.66	0.164	3.5	0.187	4.0
HSP2	7.85	0.0988	1.3	0.127	1.6
HSP3	3040	21.1	0.7	37.6	1.2
HSP4	5940	34.9	0.6	71.7	1.2
HSP5	9420	68.6	0.7	266	2.8
HSP6	9590	91.7	0.9	285	2.9
CTR1	5.28	0.127	2.4	0.161	3.0
CTR2	47	0.614	1.3	0.748	1.6

2. Linearity:

Linearity testing was performed with one reagent lot tested on one cobas e 601 analyzer with one run. One human serum sample with high analyte content above the measuring range was diluted to the lower end of the measuring range with various amounts of human serum sample without analyte content. The dilution series contained 21 steps and included concentrations between 0.25 and 11,411 mIU/mL. Samples were assayed in three replicates.

Linear, quadratic and cubic regression analyses were performed. The results of the linear regression analysis are provided below.

$$y = 0.997 * x - 0.492, r^2: 0.9977$$

The results support the claimed analytical measurement range of 1.0 to 10,000 mIU/mL.

Auto Dilution:

Verification studies were performed to determine the sample dilution recovery of the Elecsys HCG STAT immunoassay. HCG free human serum was spiked with WHO HCG standard material (6^{th} standard). These samples were automatically diluted (1:100) by the instrument, the obtained value was multiplied by 100 and the ratio of the theoretical value and the obtained value multiplied by 100 was generated.

The results are summarized in the tables below.

Sample number	Target concentration	Measured concentration	Recovery [%]
1	50000	49109	98%
2	100000	98039	98%
3	200000	204455	102%
4	300000	306419	102%
5	400000	399352	100%
6	500000	504148	101%
7	600000	643585	107%
8	700000	733311	105%
9	800000	872342	109%
10	900000	940542	105%
11	950000	996460	105%
12	1000000	1096419	110%

These results support the extended measuring range of the assay.

3. Analytical Specificity/Interference:

High Dose Hook Effect

The high-dose hook effect of the Elecsys HCG STAT assay was assessed with one reagent lot on one cobas e 601 analyzer in one-fold determination. Three (3) human serum samples were spiked with analyte (HCG) to achieve high HCG concentrations. No Hook effect was observed up to ≥ 500,000 mIU/mL of HCG.

Endogenous interference

Native human serum sample pools at three (~4 , ~3000, and 9000 mIU/mL) concentrations of hCG were tested using one reagent lot. Test samples spiked with endogenous substance and control samples with no endogenous substance were measured and compared. There was no significant interference (< ± 10% bias between test sample and control sample) up to the concentrations shown in the table below.

Potential Interferent	Highest concentration tested without significant interference
Intralipid (Lipemia)	≤ 2600 mg/dL
Bilirubin	≤ 66 mg/dL
Hemoglobin	≤ 1600 mg/dL
Rheumatoid Factor	≤ 1200 IU/mL

Cross-reactivity
Cross-reactivity of the Elecsys HCG STAT assay was determined with one reagent lot on one cobas e 601 analyzer using a human serum sample with ~4.7 mIU/mL hCG. Samples were spiked with the following potential cross-reactants: luteinizing hormone (LH), follicle stimulating hormone (FSH), or thyroid stimulating hormone (TSH). Samples with and without the potential cross-reactants were measured and cross reactivity was calculated. No cross-reactivity was observed for TSH up to 2,000 mIU/mL and FSH up to 4,000 mIU/mL. Cross reactivity for LH in the presence of hCG was found to be dependent upon LH concentration, as shown in the table below:

	Measured hCG concentration (mIU/mL)		
LH [mIU/mL]	**Without LH**	**With LH**	**Cross reactivity**
4000	5.05	32.4	0.69%
500	5.19	8.37	0.64%
450	4.75	5.70	0.21%
400	4.73	5.55	0.21%
350	4.78	5.48	0.20%
300	4.83	5.45	0.21%
250	4.79	5.36	0.23%
200	4.76	5.25	0.25%
150	4.87	5.21	0.23%
100	4.98	4.99	0.01%

Biotin Interference
Biotin interference was tested using the Elecsys HCG STAT on a cobas e 601 analyzer and three serum samples containing hCG (4.5 mIU/mL, 3,000 mIU/mL, and 10,000 mIU/mL). Test samples spiked with biotin up to 3600 ng/mL and control samples with no biotin were measured and compared. There was no significant interference (≤ ± 10% bias between test sample and control sample) observed for biotin concentrations up to 3600 ng/mL.

Common drugs interference
Potential interference from drugs was determined by comparing values obtained from serum samples containing hCG concentrations near 5 mIU/mL and near 50 mIU/mL. Test samples spiked with each of 17 common pharmaceutical compounds were measured and compared with the control sample (no interferent). There was no significant interference (≤ ± 10% bias between the test sample and the control sample) up to the concentrations illustrated below.

Potential Interferent	Highest concentration tested without significant interference (mg/dL)
Acetylcysteine	15
Acetylsalicylic acid	3.0
Ampicillin - Na	7.5
Ascorbic acid	5.25
Cefoxitin	75.0
Doxycycline	1.8
Heparin	330 IU/dL
Levodopa	0.75
Methyldopa +1.5	2.25
Metronidazole	12.3
Rifampicin	4.8
Acetaminophen	15.6
Cyclosporine	0.18
Ibuprofen	21.9
Theophylline	6.0
Phenylbutazone	32.1
Itraconazole	3.0

4. Assay Reportable Range:

   The reportable range is 1.0 -10,000 mIU/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   This assay has been standardized against the World Health Organization (WHO) 4th International Standard Chorionic Gonadotropin, Human, National Institute for Biological Standards and Control (NIBSC), code 75/589.

6. Detection Limit:

   Limit of Blank (LoB)
   For determination of LoB five analyte free samples were measured in two-fold determinations in 6 runs, distributed over ≥ 3 days, with two (2) different lots on one (1) cobas e 601 analyzer. In total 60 measured values of analyte free samples were obtained per lot. The results provided support LoB of 0.5 mIU/mL

Limit of Detection (LoD)
For determination of LoD five samples with low-analyte concentration (from 0. 5 mIU/mL up to 1.9 mIU/mL) were measured in 2-fold determination in 6 runs, distributed over ≥ 3 days, with 2 different lots on one cobas e 601 analyzer. In total 60 measured values of samples with low analyte concentrations were obtained per lot. The results provided support LoD of 1 mIU/mL.

Limit of Quantitation (LoQ)
For the determination of LoQ, 2 lots were evaluated, each with 5 human serum samples covering the range between 0.57 and 1.8 mIU/mL. Each sample was measured in 5 replicates with one run per day over 5 days on one cobas e 601 analyzer. The results support the claimed LoQ of 1 mIU/mL.

7. Assay Cut-Off:

   Not Applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   A method comparison study between the candidate Elecsys HCG STAT assay and the predicate device, Elecsys HCG STAT assay (k002148), was conducted internally using both the predicate and candidate assays on the cobas e 601 analyzer. One hundred thirty-one (131) samples spanning the range between 1.32 mIU/mL and 9848 mIU/mL were tested with one run per sample. Passing-Bablok regression analysis of the results is provided below.

	Passing/Bablok regression analysis
N	131
Range Tested (predicate)	1.32 – 9848 mIU/mL
Slope	1.012 (95% CI: 1.010, 1.014)
Intercept	-0.970 mIU/mL (95% CI: -2.69, -0.2)
Correlation coefficient r	1.000

2. Matrix Comparison:
   A matrix comparison study was performed to evaluate matrices suitable for use with the Elecsys HCG STAT assay. Native human serum samples drawn into serum primary tubes (reference) were compared to matched Li-Heparin, K2-EDTA or K3-EDTA plasma samples. The samples were run on the cobas e 601 analyzer. The results were assessed using Passing/Bablok regression analysis.

Serum/Li-Heparin Plasma Summary Results

	Passing/Bablok regression analysis
N	56
Range	1.63 – 9975 mIU/mL
Slope	0.982 (LCL 95%: 0.978 and UCL 95%: 0.990)
Intercept	0.001 mIU/mL (LCL 95%: -1.85 and UCL 95%: 0.989)
Correlation coefficient r	1.00

Serum/K2-EDTA Plasma Summary Results

	Passing/Bablok regression analysis
N	60
Range	2.24 – 9463 mIU/mL
Slope	0.983 (LCL 95%: 0.976 and UCL 95%: 0.990)
Intercept	0.058 mIU/mL (LCL 95%: -1.63 and UCL 95%: 4.00)
Correlation coefficient r	0.998

Serum/K3-EDTA Plasma Summary Results

	Passing/Bablok regression analysis
N	45
Range	1.33 – 9436 mIU/mL
Slope	0.973 (LCL 95%: 0.963 and UCL 95%: 1.002)
Intercept	-1.76 mIU/mL (LCL 95%: -18.7 and UCL 95%: 0.036)
Correlation coefficient r	0.997

B Clinical Studies:

1. Clinical Sensitivity:

   Not Applicable.

2. Clinical Specificity:

   Not Applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not Applicable.

C Clinical Cut-Off:

Not Applicable.

D Expected Values/Reference Range:

The reference range was established in K002148.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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