510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k162606

B. Purpose for Submission:

Adding a previously cleared assay on a new a instrument platform.

C. Measurand:

Thyroid-stimulating hormone (TSH)

D. Type of Test:

Quantitative, electrochemiluminescence immunoassay

E. Applicant:

Roche Diagnostics Corp

F. Proprietary and Established Names:

Elecsys TSH assay
Cobas e 801 Immunoassay analyzer

G. Regulatory Information:

Product Code	Regulation Name	Classification	Regulation Section	Panel
JLW	Thyroid stimulating hormone test system	Class II	21 CFR § 862.1690	Chemistry 75
JJE	Discrete photometric chemistry analyzer for clinical use	Class I	21 CFR § 862.2160	Chemistry 75

H. Intended Use:

1. Intended use(s):
   See indications for use

2. Indication(s) for use:

   cobas e 801 immunoassay analyzer is intended for the in-vitro determination of analytes in body fluids.

   Elecsys TSH immunoassay is intended for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in diagnosis of thyroid or pituitary disorders. The Elecsys TSH immunoassay is an electrochemiluminescence immunoassay "ECLIA", which is in intended for use on the cobas e immunoassay analyzers.

3. Special conditions for use statement(s):

   For prescription use.

4. Special instrument requirements:

   Cobas e 801 Immunoassay analyzer

I. Device Description:

The cobas e 801 immunoassay analyzer is a fully automated, software controlled analyzer system for in vitro determination of analytes in human body fluids. It is part of the **cobas** 8000 modular analyzer series cleared under k100853. It uses electrochemiluminescent technology for signal generation and measurement. It is a modified version of the cobas e 601 analyzer module, part of the cobas 6000 modular analyzer.

The Roche Elecsys TSH assay contains the following reagents:

The Elecsys TSH assay employs monoclonal antibodies specifically directed against human TSH. The antibodies labeled with ruthenium complex a) consist of a chimeric construct from human and mouse-specific components.

The reagents include:

M Streptavidin-coated microparticles, 1 bottle, 14.1 mL: Streptavidin-coated microparticles 0.72 mg/mL, preservative.

R1 Anti-TSH-Ab~biotin, 1 bottle, 15.8 mL: Biotinylated monoclonal anti-TSH antibody (mouse) 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-TSH-Ab~Ru(bpy) , 1 bottle, 13.9 mL: Monoclonal anti-TSH antibody (mouse/human) labeled with ruthenium complex 1.2 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

Total duration of the assay is 18 min, sandwich principle.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Elecsys 2010
   Elecsys TSH assay

2. Predicate 510(k) number(s):

   k961491

3. Comparison with predicate:

Similarities- Analyzer		
Item	**Candidate Device: cobas e801 analyzer (k162606)**	**Predicate device: Elecsys 2010 (k961491)**
Intended Use	Same	Fully automated immunoassay analyzer intended for the in vitro determination of analytes in body fluids.
Measurement principle	Same	Electrochemiluminescence immunoassay method (ECLIA)
Workflow principle	Same	Batch or random access
Temp. control	Same	Incubation at 37°C.
Probe cleaning	Same	Automatic for reagent probe
Functions performed	Same	Data input, sample processing, result calculation, result reporting, quality control

Differences- Analyzer		
Item	**Candidate Device: cobas e801 analyzer (k162606)**	**Predicate device: Elecsys 2010 (k961491)**
Throughput	300 tests/hour/module	86 tests/hour/module
Typical sample volumes	4-60 µL	10-50µL
Sample handling system	Input and transport of samples using universal sample racks, modular sample buffer input, core/transportation unit and STAT port.	Via sample disk or racks

Differences- Analyzer		
Item	**Candidate Device: cobas e801 analyzer (k162606)**	**Predicate device: Elecsys 2010 (k961491)**
Sample capacity on board	300	Disc:30; rack: 75
Reagent volume	6-60 µL	10-190 µL
Reagent container	Plastic bottles with changes in materials, geometry and volume	Plastic bottles closed via snap caps
Onboard storage temperature	5-10 °C	18-22 °C
Reagent bottle/Cassette identification	RFID	2-d Barcode
Software	cobas 8000 modular System Software	Elecsys 2010 Software
Configuration	One PC and one core in combination with several e-modules or c analytical modules	Stand alone

Similarities and Differences- Reagent		
Item	**Candidate Device: Elecsys TSH on cobas e801 analyzer (k162606)**	**Predicate Device: Elecsys TSH on Elecsys 2010 (k961491)**
Intended Use	same	Immunoassay for the in vitro quantitative determination of thyroid stimulating hormone in human serum and plasma
Antibody/ Reagents	Same	Biotinylated monoclonal anti-TSH antibody (mouse) Monoclonal anti-TSH antibody (mouse/human) labeled with ruthenium complex Streptavidin –coated microparticles
Measuring Range	same	0.005-100 µIU/mL
Measurement principle	same	Electrochemiluminescence immunoassay (ECLIA) method
Sample size	50 µL of sample	30µL of sample
Sample Types	Serum, serum with separating gel, Li-heparin, K2EDTA, and K3EDTA	Serum, serum with separating gel, Li-heparin, K2EDTA, K3EDTA, Sodium citrate and NaF/K oxalate

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

CLSI EP5, Evaluation of Precision Performance of Quantitative Measurement Method, Version A2, 2005.

CLSI EP6, Evaluation of the Linearity of Quantitative Measurement Procedures, Version A, 2009.

CLSI EP9, Method Comparison and Bias Estimation using patient samples, Version A3, 2010.

CLSI EP17, Evaluation of Detection Capability of Clinical Laboratory Measurement Procedures, Version A2, 2012.

IEC 61010-2-101, Safety requirements for electrical equipment for measurement, control and laboratory use- Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment, 2015.

L. Test Principle:

Incubation of sample, a biotinylated monoclonal TSH-specific antibody and a monoclonal TSH-specific antibody labeled with a ruthenium complex react to form a sandwich complex (first incubation). After streptavidin-coated magnetic microparticles are added to the incubate the sandwich complexes are bound in the second incubation step to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is then aspirated into the measuring cell where the microparticles are magnetically captured on the surface of the electrode. Unbound substances are removed by washing with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured and amplified by a photomultiplier .

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   Precision of the Elecsys TSH assay was evaluated on cobas e801 immunoassay analyzer according to CLSI document EP5-A3. Three serum based controls and 11 levels of serum samples (Serum 1 to 5 and 11 were pooled samples, serum 6-10 were spiked pooled samples). The samples were tested in duplicate, twice per day for 21 days (N=84). Results are summarized in the tables below:

Sample	n	Mean µIU/mL	Within-run		Total	
			SD µIU/mL	CV%	SD µIU/mL	CV%
PC Universal 1	84	1.41	0.0197	1.4	0.0301	2.1
PC Universal 2	84	8.18	0.132	1.6	0.207	2.5
PreciControl TS	84	0.184	0.00325	1.8	0.00417	2.3
Serum 1	84	0.00851	0.000600	7.1	0.000962	11.3
Serum 2	84	0.209	0.00338	1.6	0.00520	2.5
Serum3	84	1.88	0.0264	1.4	0.0432	2.3
Serum 4	84	51.8	0.653	1.3	1.05	2.0
Serum 5	84	90.0	1.24	1.4	1.75	1.9

b. Linearity/assay reportable range:

Linearity of the Elecsys TSH assay was assessed on the cobas e 801 Immunoassay Analyzer using 3 different lot reagents according to CLSI EP6-A. A high serum sample was serially diluted into 10 concentrations with the TSH specimen diluent (Diluent MultiAssay) to obtain a total of 12 TSH samples (0.00, 0.004, 0.203, 0.678, 2.03, 5.09, 10.2, 25.4, 33.9 50.9, 72.7, 102 µIU/mL) ranging from 0-102 µIU/mL throughout the measuring range. All 12 samples were assayed in triplicate. The results from 3 lots of reagent yielded similar results. One representative lot is summarized in the table below.

The measured values were plotted against the target values and the regression results support the sponsor's claim.

Linear Regression Equation and Correlation Coefficient	
Slope	0.952
Intercept	-0.00272
r	0.9986

The sponsor claims a measuring range of 0.005-100 µIU/mL for the Elecsys TSH assay.

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

Traceability:

This method is traceable to the 2nd IRP WHO Reference Standard 80/558.

Controls and Calibrator:

PreciControl Universal (cleared under k090541) and PreciControl TS (cleared under k140534) are the recommended controls to be used with the Elecsys TSH assay.

The Roche Elecsys TSH CalSet (cleared under k060754) is the recommended calibrator to be used with the Elecsys TSH assay.

Reagent Stability:

The sponsor provided new real time stability study protocol and acceptance criteria, and these were reviewed and found to be acceptable. The reagent is stable when stored unopened at +2°C to +8°C or onboard (5-10°C) for 16 weeks.

d. Detection limit:

The Limit of Blank (LoB) of the Elecsys TSH assay on the cobas e 801 Immunoassay Analyzer was determined according to CLSI EP17-A2 as the 95th percentile of measurements of blank samples on the cobas e 801 analyzer. One blank serum sample with no detectable levels of TSH were assayed per day, 10 replicates per run, using three lots of reagent over six days for a total of 60 replicates. The LoB was calculated to be 0.0025 µIU/mL.

The Limit of Detection (LoD) of the Elecsys TSH assay was determined as recommended in CLSI EP17-A2 by using five low-level TSH native serum samples (0.000967- 0.00112 µIU/mL). All samples were assayed in duplicate, one run per day over six days, for a total of 20 runs using three lots of reagents (n=60) on the cobas e 801 instrument. The LoD was calculated to be 0.005 µIU/mL using the following equation: LoD = LoB + 1.653 SD.

The Limit of Quantitation (LoQ) was determined using functional sensitivity for five low-level native TSH serum samples (0.0078 to 0.064µIU/mL). All samples were assayed in five replicates , one run per day, for over five days, on the cobas e 801 instrument, using three reagent lots (n=75). Functional sensitivity was based on the within lab precision of 20% CV and was determined to be 0.005 µIU/mL.

The results of the detection limits are summarized in the table below:

LoB	**LoD**	**LoQ**
0.0025 µIU/mL	0.005 µIU/mL	0.005 µIU/mL

This study supports the claimed assay measuring range of 0.005 to 100 µIU/mL.

e. Analytical specificity:

An interference study was conducted to evaluate the effect of endogenous interfering substances using the Elecsys TSH on the cobas e 801 Immunoassay analyzer. Three serum samples containing low (pooled sera), medium (pooled spiked sera), and high (pooled spiked sera) concentrations of TSH were tested.

The spiked sample (interference pool) was then diluted in 10% increments. The recovery was determined by testing a control sample without the interferent and comparing it to the value obtained from a test sample in which the potential interferent had been added. The sponsor defined significant interference as follows:

Sample with concentration of 0.005 to 0.2 µIU/mL: > ± 0.02 µIU/mL
Sample with concentration of > 0.2 to 100 µIU/mL: > ± 10%

No significant interference was observed for the substances and concentrations listed below:

Potential interfering endogenous substances	**Highest interferent concentration tested at which no significant interference was observed**
Intralipid (Lipemia)	2000 mg/dL
Biotin	56.0 ng/mL
Bilirubin	66.0 mg/dL
Hemoglobin	1000 mg/dL
Rheumatic Factor	1500 IU/mL
Human IgG	2.80g/dL
Human IgM	0.500 g/dL

In addition, the sponsor states the following in the limitation section in the package insert:
"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."

Drug interference:

The effect on quantitation of analyte in the presence of drugs was determined by comparing values obtained from samples spiked with 29 pharmaceutical compounds spiked into two human serum samples (pooled serum samples, native) and tested on the Elecsys TSH assay on the cobas e 801 Immunoassay Analyzer. The analyte concentrations of the samples were approximately 0.3 and 8 µIU/mL. The sponsor defined non-significant interference as recovery within ±10%.

Potential interfering exogenous substances	**Highest interferent concentration tested at which no significant interference was observed**
Acetylcystein	553 mg/dL
Ampicillin-Na	1000 mg/dL
Ascorbic acid	300 mg/dL
Cyclosporine	5 mg/dL
Cefoxitin	2500 mg/dL
Heparin	5000 U

Potential interfering exogenous substances	Highest interferent concentration tested at which no significant interference was observed
Levodopa	20 mg/dL
Methyldopa +1.5	20 mg/dL
Metronidazole	200 mg/dL
Phenylbutazone	400 mg/dL
Doxycycline	50 mg/dL
Acetylsalicylic Acid	1000 mg/dL
Rifampicin	60 mg/dL
Acetaminophen	200 mg/dL
Ibuprofen	500 mg/dL
Theophylline	100 mg/dL
Amiodarone	200 mg/L
Carbimazole	30 mg/L
Fluocortolone	100 mg/L
Hydrocortisone	200 mg/L
Iodide	0.2 mg/L
Levothyroxine	0.25 mg/L
Liothyronine	0.015 mg/L
Methimazole	80 mg/L
Octreotide	0.3 mg/L
Prednisolone	100 mg/L
Propanolol	240 mg/L
Propylthiouracil	60 mg/L
Perchlorate	2000 mg/L

A cross-reactivity study was conducted according to CLSI-EP7-A2 to evaluate the potential cross-reactivity of the assay. The potential cross-reactants were added at defined concentrations to native human sera with approximate concentrations of 0, 12.5, 25, 50 and 100 µIU/mL and analyzed with Elecsys TSH on the cobas e 801 analyzer. Results from these spiked serum samples were matched against the unspiked references and the % cross-reactivity was calculated as follows:

% cross-reactivity = (mean concentration of spiked sample – mean concentration of unspiked sample/spiked concentration) x 100

The following cross-reactivities were found, tested with TSH concentrations of 0.3 µIU/mL and 8 µIU/mL.

Cross-reactant	Concentration Tested mU/mL	Cross-reactivity %
LH	10,000	<0.038
FSH	10,000	<0.080
hGH	1,000	0.00
hCG	50,000	0.00

Hook effect: High dose hook effect of the Elecsys TSH was assessed on the cobas e 801 analyzer with three serum samples. The samples were spiked with analyte to achieve high TSH concentration. The hook concentration reported corresponds to the highest analyte concentration that generates a signal ≥10% above the upper limit of the measuring range. There was no high dose effect observed at TSH concentrations equal or higher than (≥) 1,000 µIU/mL.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed to compare TSH on the Elecsys 2010 analyzer (predicate) and the cobas e 801 analyzer. A total of 130 samples were measures with the Elecsys TSH immunoassay on the analyzer in singlicate covering the mearing range; mean values ranged from 0.009-92.6 µIU/mL. Two out of 130 were spiked. Passing/Bablok and Linear regression analyses were performed according to CLSI EP09-A3. The data is summarized in the table below:

n	Passing/Bablok Regression	Linear Regression	Pearson Correlation Coefficient	Sample Range On Elecsys 2010 (µIU/mL)
130	y = 0.936x – 0.003	y = 0.958x – 0.052	0.999	0.005 – 85.9

b. Matrix comparison:

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys TSH Immunoassay was determined by comparing values obtained from samples (single donors, native as well as spiked) drawn into Serum, Li-Heparin, K2-EDTA and K3-EDTA plasma tubes. A total of 56 serum/plasma pairs were tested in singleton with one reagent lot on one cobas e 801 immunoassay analyzer.

Data were evaluated using a regression analysis according to Passing/Bablok. The data and regression analysis are summarized below:

	Lithium Heparin	**K2-EDTA**	**K3-EDTA**
n	56	56	56
Sample Range Tested	0.0147 – 92.5 µIU/mL	0.0147 – 92.5 µIU/mL	0.0147 – 92.5 µIU/mL
Slope	1.001	0.994	0.983
Y-Intercept (µIU/mL)	-0.00634	-0.00600	-0.0229
Correlation Coefficient	0.999	0.999	0.999

The results of this study support the use of samples drawn into serum, Li-Heparin, K2-EDTA and K3-EDTA plasma tubes with the Elecsys TSH assay.

3. Clinical studies:

   a. Clinical Sensitivity:

   Not applicable

   b. Clinical specificity:

   Not applicable

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

   Not applicable

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   0.270-4.20 µIU/mL

   These values correspond to the 2.5^{th} and 97.5^{th} percentiles of results obtained from a total of 516 healthy test subjects examined. Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

N. Instrument Name:

Cobas e801 Chemistry Analyzer

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___x_____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No ___x_____

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ___x_____ or No _____

3. Specimen Identification:

   Barcode

4. Specimen Sampling and Handling:

   Input and transport of samples using universal sample racks, modular sample buffer input, core/transportation unit and STAT port.

5. Calibration:

   It is recommended to perform calibration once per reagent lot using fresh reagent (i.e. not more than 24 hours since the cobas e pack was registered on the analyzer). Renewed calibration is recommended after 12 weeks when using the same reagent lot, after 28 days when using the same cobas e pack on the analyzer and as required: e.g. quality control findings outside the defined limits.

6. Quality Control:

   The sponsor recommends running various concentrations of controls at least once every 24 hours when the test is in use, once per cobas e pack. Values obtained should fall

within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

The software documentations were reviewed and found to be acceptable. The firm provided documentation to support the devices was designed, developed and is under good software lifecycle processes.

Q. Proposed Labeling:

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

R. Conclusion:

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