

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

A. 510(k) Number:

k062581

B. Purpose for Submission:

New device

C. Measurand:

Thyroid stimulating hormone (TSH)

D. Type of Test:

Quantitative, Chemiluminescent Immunoassay

E. Applicant:

Olympus America, Inc.

F. Proprietary and Established Names:

Olympus TSH Reagent, Calibrator and Control and AU3000i Immunoassay System

G. Regulatory Information:

1. Regulation section:

21CFR §862.1690-Thyroid stimulating hormone test system.

21 CFR §862.1150-Calibrator.

21 CFR §862.1660-Quality control material (assayed and unassayed).

21 CFR §862.2160-Discrete Photometric Chemistry Analyzer for Clinical Use

2. Classification:

2, 2, 1 reserved, 1 respectively

3. Product code:

JLW Radioimmunoassay, Thyroid-Stimulating Hormone

JIS Calibrator, Primary

JJX Single (Specified) Analyte Controls (Assayed and Unassayed)

JJE Analyzer, Chemistry (Photometric, Discrete), For Clinical Use

4. Panel:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indication for use below

2. Indication(s) for use:

The Olympus thyroid stimulating hormone (TSH) assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of TSH levels in human serum and plasma using the Olympus AU3000i™ Immunoassay System.

Measurements of TSH produced by the anterior pituitary are used in the diagnosis of thyroid or pituitary disorders.

The Olympus TSH Calibrator is used for calibrating the quantitative Olympus TSH Assay on the Olympus AU3000i Immunoassay System.

The Olympus TSH Control is used for quality control of the Olympus TSH test system on the Olympus AU3000i Immunoassay System.

The Olympus AU3000i Immunoassay System is a chemiluminescent discrete photometric chemistry analyzer for the quantitative determination of analytes in human serum and plasma.

3. Special conditions for use statement(s):
Prescription use only
4. Special instrument requirements:
Olympus AU3000i™ Immunoassay System.

I. Device Description:

Olympus TSH reagent kit

R1: Paramagnetic particles coated with murine monoclonal anti-TSH antibody, Tris buffer, pH 7.3 with protein stabilizers and preservative.

R2: Alkaline phosphatase labeled murine monoclonal anti-TSH antibody, MES buffer, pH 6.5 with protein stabilizers and preservative.

CALIBRATOR: TSH prepared in bovine matrix with preservative.

CONTROL: TSH prepared in human matrix with preservative.

The components used in this product contain materials of human or animal origin.

Components derived from human blood have been tested by an FDA approved method and found to be non-reactive for HBsAg, anti-HCV, and anti-HIV-1/HIV-2.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Reagent: Roche Elecsys® TSH Assay
Calibrator: Roche Elecsys® TSH CalSet
Control: Roche Elecsys® PreciControl TSH
Analyzer: Roche Elecsys® 2010 analyzer
2. Predicate 510(k) number(s):
k961491, k060754, k962573, k961481
3. Comparison with predicate:

Item	Similarities	
	AU3000i with TSH	Roche Elecsys® TSH
Intended Use	Quantitative determination of thyroid stimulating hormone (TSH) levels in human serum/plasma	Immunoassay for the in vitro quantitative determination of thyrotropin in human serum and plasma.
Traceability	WHO	WHO
Detection/Operating Principle	Chemiluminescence	Chemiluminescence
Assay Methodology	Sandwich immunoassay	Sandwich immunoassay
Solid Phase	Micro-particle	Micro-particle
Sample Type	Serum and plasma	Serum and plasma
Antibody	Monoclonal anti-TSH mouse antibody	Monoclonal anti-TSH mouse antibody
Analyzer Reagents	On-board Storage Bar-coded (1-D & 2-D) reagent, calibrator & control Cap/septum for increased reagent	On-board Storage Bar-coded (1-D & 2-D) reagent, calibrator & control Cap/septum for increased reagent

Similarities		
Item	AU3000i with TSH	Roche Elecsys® TSH
	stability and evaporation control	stability and evaporation control
Reagent, Calibrator and Control storage form	Liquid	Liquid
Calibration and Control Stability	Unopened <ul style="list-style-type: none"> At 2-8°C up to the stated expiration date Opened <ul style="list-style-type: none"> 28 days / 4 weeks at 2-8°C 	Unopened <ul style="list-style-type: none"> At 2-8°C up to the stated expiration date Opened <ul style="list-style-type: none"> 28 days / 4 weeks at 2-8°C
Control levels and target concentration range	One Euthyroid/Hyperthyroid threshold	One Euthyroid/Hyperthyroid threshold
Control constituents	Single	Single
Control Matrix	Human serum with added antigen	Human serum with added antigen
Analyzer System	Fully automated Random access Computer controlled Stat capability	Fully automated Random access Computer controlled Stat capability
Analyzer/User Interface	Keyboard/touch screen control Colored touch screen monitor Stationary barcode scanners Graphical user interface On line help	Keyboard/touch screen control Colored touch screen monitor Stationary barcode scanners Graphical user interface On line help
Analyzer Consumables	Disposable reaction vessels Disposable sample tips	Disposable reaction vessels Disposable sample tips
Analyzer Sample Detection	Liquid Level Detection Clot Detection	Liquid Level Detection Clot Detection
Analyzer Host Interface	RS232C bidirectional	RS232C bidirectional
Differences		
Item	AU3000i with TSH	Roche Elecsys® TSH
Instrument Required	Olympus AU3000i™ Immunoassay System	Roche Elecsys and Modular analytics immunoassay analyzers.
Traceability	WHO 3 rd IS 81/565	WHO 2 nd IRP 80/558
Calibrator levels and target Concentration	One Cal: 13 mIU/L	Two Cal 1: 0 mIU/L Cal 2: 1.5 mIU/L
Solid phase binding principle	Direct coating	Biotin and streptavidin
Assay Range	0.001 – 130 mIU/L	0.005 – 100 mIU/L
Calibrator Matrix	Bovine serum human pituitary TSH	Horse serum with added recombinant TSH
Analyzer Sample Volume	10 – 100 µl	10 – 50 µl
Analyzer Reagent Positions	24 reagent positions 2 diluent/pretreatment positions	15 reagent positions 2 diluent/pretreatment positions
Analyzer Throughput	240 results/hour	88 results/hour

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

CLSI - Evaluation of Precision Performance of Clinical Chemistry Devices - EP05-A2

CLSI - Interference Testing in Clinical Chemistry - EP07-A2

CLSI - Method Comparison and Bias Estimation Using Patient Samples - EP09-A2

CLSI - How to Define and Determine Reference Intervals in the Clinical Laboratory - EP28-A2

CLSI - Clinical Evaluation of Immunoassays - I/LA21-A

IEC - Medical Devices - Risk Analysis - EN 14971

L. Test Principle:

The Olympus TSH assay is a two-step paramagnetic particle enzyme immunoassay. It is based on the sandwich principle and used to quantitate TSH in serum/plasma.

The Olympus TSH assay reagent and sample are added to the assay cuvette in the following sequence:

1. Samples are incubated first with a monoclonal anti-TSH antibody bound to paramagnetic particles.
2. After a washing step, a second monoclonal anti-TSH antibody conjugated with alkaline phosphatase is added. The TSH reacts with the paramagnetic particles and the conjugated antibody to form a sandwich complex. Washing steps remove the unbound material.
3. The chemiluminescent substrate is added to the assay cuvette and reacts with the bound alkaline phosphatase (ALP). Light generated by the reaction is measured by the luminometer. The light emission is proportional to the quantity of TSH in the sample.
4. Results are calculated from a pre-defined calibration curve. The Olympus AU3000i system automatically calculates the TSH concentration of each sample in mIU/L or μ IU/mL.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision was determined using pooled human sera according to CLSI protocol EP5-A: 2 per day for 20 days (n=80).

Sample	Within run			Total	
	Mean [mIU/L]	SD [mIU/L]	CV [%]	SD [mIU/L]	CV [%]
1	0.119	0.003	2.7	0.003	2.9
2	2.145	0.047	2.2	0.128	6.0
3	46.255	1.070	2.3	1.696	3.7

b. *Linearity/assay reportable range:*

Assay measuring range is approximately 0.001 – 130 mIU/L.

To assess performance of the device, four patient samples at various concentrations were serially diluted with a prepared standard solution built with an artificial matrix. The recovery of each sample was measured using the Olympus TSH Assay. Percent recovery was calculated as follows:

$$\% \text{ Recovery} = \frac{\text{Observed value}}{\text{Expected value}} \times 100$$

Results are summarized below:

Sample	Dil.	Expected [mIU/L]	Observed [mIU/L]	Recovery [%]	Total Mean [%]
1	-	-	134.835	100.00	93.68
	1:2	67.418	67.233	99.73	
	1:4	33.709	31.190	92.53	
	1:8	16.854	15.454	91.69	
	1:16	8.427	7.306	86.70	
	Mean	-	-	92.66	
2	-	-	29.404	100.00	
	1:2	14.702	15.373	104.57	
	1:4	7.351	6.878	93.56	
	1:8	3.6755	3.301	89.81	
	1:16	1.8378	1.581	86.01	
	Mean	-	-	93.49	
3	-	-	2.141	100.00	
	1:2	1.071	1.046	97.72	
	1:4	0.2676	0.465	86.86	
	1:8	0.5353	0.238	88.86	
	1:16	0.1338	0.120	90.03	
	Mean	-	-	90.87	
4	-	-	0.459	100.00	
	1:2	0.2295	0.229	99.66	
	1:4	0.1148	0.113	98.82	
	1:8	0.0574	0.056	97.49	
	1:16	0.0287	0.027	94.86	
	Mean	-	-	97.70	

Four human serum samples in the range of 0.459 to 134.835 mIU/L of TSH were diluted and assayed. The recoveries ranged from 86.01 % to 104.57 % with a mean of 93.68 %. Therefore, the Olympus TSH assay can recover diluted analyte in serum within ± 10 % of the total mean.

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The TSH calibrator is traceable to the WHO 3rd International Standard 81/565. The calibration material is prepared by creating a master calibrator from the reference material and bovine serum matrix in which the value assignment is verified with 1 instrument, 3 runs, 6 replicates per run. Lot specific master curve and calibrator value assignment are determined on 1 instrument, 3 runs, 15 replicates per run. Once open, the calibrator is stable at 2-8 °C for 28 days, and unopened until the stated expiration date which is validated with ongoing real time stability studies.

The TSH Control target concentration range is set at the euthyroid/hyperthyroid threshold. Value assignments are determined on 3 instruments, 3 runs, 3 days, 5 replicates per run. Once open, the control is stable at 2-8 °C for 28 days and unopened until the stated expiration date which is validated with ongoing real time stability studies.

- d. *Detection limit:*
Analytical Sensitivity
The lowest detectable level on an Olympus AU3000i analyzer was calculated as 0.0002 mIU/L. The lower end of the measuring range for this device was

determined to be 0.001 mIU/L.

The lowest detectable level represents the lowest measurable level of TSH that can be distinguished from zero. It is calculated as the absolute mean plus two standard deviations of 20 replicates of an analyte free sample.

Functional sensitivity

The functional sensitivity on an Olympus AU3000i analyzer was calculated as 0.0013 mIU/L.

The functional sensitivity is the lowest TSH concentration that can be measured reproducibly with an interassay CV of 20 %.

e. Analytical specificity:

Analytical Specificity

The following cross-reactivities have been determined for the assay by adding a pre-defined amount of potential cross-reactants to a human sample.

The AU3000i TSH assay has no significant cross reactivity with the following substances, at the concentration levels listed.

- FSH - ≤ 1500 mIU/mL
- LH - ≤ 2500 mIU/mL
- hCG - $\leq 500,000$ mIU/mL

Interfering Substances

Results of studies conducted to evaluate the susceptibility of the method to interference were as follows:

Icterus: Interference less than 10% up to 40 mg/dL (or 684 μ mol/L) bilirubin.

Hemolysis: Interference less than 5% up to 5 g/L hemoglobin

Lipemia: Interference less than 3% up to 10 g/L Intralipid®

Rheumatoid factor: No significant interference up to 2010 IU/mL of rheumatoid factor.

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Patient serum/plasma samples were used to compare the Olympus TSH assay on the Olympus AU3000i analyzer against another commercially available TSH assay using CLSI protocol EP9-A. Results of regression by Passing-Bablok analysis were as follows:

N	Range of concentrations [mIU/L]	Intercept [mIU/L]	Slope	Correlation Coefficient
127	0.005 - 136.630	-0.0046	0.935	0.9931

b. Matrix comparison:

Serum versus plasma study was carried out by collecting blood from at least 10 donors into various blood collection tubes and measuring the TSH concentration in each. The blood collection tubes tested were serum, EDTA plasma, and lithium heparin plasma.

The mean results from each tube were compared by using a paired t-test (95% confidence interval) and % bias.

Collection Tubes	T-Test Null Hypothesis	Mean % Bias
Serum vs. Li-H	Accepted	N/A
Serum vs. EDTA	Rejected	-3.7%

The t-test showed no statistical difference between serum and lithium heparin plasma. In accordance with the procedures no further analysis was necessary and lithium heparin plasma was accepted as a suitable sample type.

The t-test showed a statistical difference between serum and EDTA plasma. The sponsor determined that the mean % bias between these matrices (-3.7%) was acceptable because it was lower than their predetermined total allowable error for the TSH assay (24.6%).

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:
Reference range defined by National Institutes of health:
0.40 - 4.00 mIU/L

N. Instrument Name:

Olympus AU3000i™ Immunoassay System.

O. System Descriptions:

1. Modes of Operation:
The Olympus AU3000i Immunoassay System is a chemiluminescent discrete random access photometric chemistry analyzer.
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:

Sequential mode, Rack barcode scan mode, Sample barcode scan mode,
download test order and patient identification

4. Specimen Sampling and Handling:

Serum or blood plasma, Urine, Others (RBC, CSF) in sample tubes or cups held
in various sample racks

5. Calibration:

Calibration types

Polygonal curve

Index by cut-off value

Calibration parameters

Maximum of 16 master calibration points per test

6. Quality Control:

QC samples

Maximum of 180 internal, Olympus-supplied controls

Maximum of 99 external, non-Olympus controls

Maximum of 6 levels per test can be used

QC checks

Shewhart X-R management (within day-to-day deviation)

Multirule (Westgard method)

Twin plot

**P. Other Supportive Instrument Performance Characteristics Data Not Covered In
The “Performance Characteristics” Section above:**

Not applicable

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.