510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number
K233050

B Applicant
Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names
ADVIA Centaur TSH3-Ultra II (TSH3ULII)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JLW	Class II	21 CFR 862.1690 - Thyroid Stimulating Hormone Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:
Modification of existing device

B Measurand:
Thyroid Stimulating Hormone (TSH)

C Type of Test:
Quantitative, chemiluminescence immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The ADVIA Centaur® TSH3-Ultra II (TSH3ULII) assay is for in vitro diagnostic use in the quantitative determination of thyroid-stimulating hormone (TSH, thyrotropin) in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur® XP system. Measurements of thyroid stimulating hormone produced by the anterior pituitary are used in the diagnosis of thyroid or pituitary disorders.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Special Instrument Requirements:

ADVIA Centaur® XP System

IV Device/System Characteristics:

A Device Description:

ADVIA Centaur TSH3-Ultra (TSH3-UL) kit consists of the following reagents:

- Ultra-Lite Reagent- bovine serum albumin (BSA) conjugated to monoclonal anti- TSH (~0.3 µg/mL) labeled with acridinium ester in HEPES buffered saline, mouse IgG, BSA, goat serum, surfactant, and preservatives.
- Solid Phase Reagent - anti-fluorescein monoclonal mouse antibody covalently linked to paramagnetic particles (PMP) (~85 µg/mL) in HEPES buffered saline, BSA, goat serum, surfactant, and preservative.
- Ancillary Well Reagent – Fluorescein isothiocyanate conjugated to monoclonal anti-TSH (~3 µg/mL) in HEPES buffered saline, mouse IgG, BSA, goat serum, surfactant, and preservative.

Product Materials/Contents:

The ADVIA Centaur TSH3ULII assay kit is comprised of the following components:

- 5 Ready Pack primary reagent packs containing TSH3ULII Lite Reagent, Solid Phase, and Ancillary Well Reagent (500 tests).
- Advia Centaur TSH3ULII master curve card.
- 2 vials CAL 3A low calibrator.
- 2 vials CAL 3A high calibrator.
- ADVIA Centaur CAL 3A calibrator assigned value cards and barcode labels.

Materials Required but Not Provided

The ADVIA Centaur TSH3ULII assay requires ADVIA Centaur Wash 1 as it is utilized in the Assay Procedure (see section below).

B Principle of Operation:

This assay is a third-generation assay that employs anti-FITC monoclonal antibody covalently bound to paramagnetic particles, an FITC-labeled anti-TSH capture mouse monoclonal antibody, and a tracer consisting of a proprietary acridinium ester and an anti-TSH mouse monoclonal antibody conjugated to bovine serum albumin (BSA) for chemiluminescent detection.

A direct relationship exists between the amount of TSH present in the patient sample and the amount of relative light units (RLUs) detected by the system.

V Substantial Equivalence Information:

A Predicate Device Name(s):

ADVIA Centaur TSH3-Ultra (TSH3-UL)

B Predicate 510(k) Number(s):

K083844

C Comparison with Predicate(s):

Device & Predicate Device(s):	K233050	K083844
Device Trade Name	ADVIA Centaur TSH3-Ultra II (TSH3ULII)	ADVIA Centaur TSH3-Ultra (TSH3-UL)
General Device Characteristic Similarities		
Intended Use/Indications For Use	Quantitative determination of thyroid-stimulating hormone (TSH, thyrotropin) in human serum and plasma. Measurements of thyroid stimulating hormone produced by the anterior pituitary are used in the diagnosis of thyroid or pituitary disorders.	Same
General Device Characteristic Differences		
Solid Phase Antibody	FITC-labeled mouse monoclonal anti-TSH antibody and mouse monoclonal anti-fluorescein antibody linked to paramagnetic particles.	Mouse monoclonal anti-fluorescein antibody linked to paramagnetic particles.

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3; 2019 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition

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

CLSI EP28-A3c (Formerly C28-A3c); Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline -Third Edit

CLSI EP07 3rd Edition; Interference Testing in Clinical Chemistry.

CLSI EP06 2nd Edition; 7-306 Evaluation of the Linearity of Quantitative Measurement

CLSI EP25-A (Replaces EP25-P); Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   Precision studies were conducted following the recommendations in CLSI EP05-A3 to estimate repeatability and within-laboratory precision.

   Repeatability
   The study was run on the candidate device, using 3 reagent lots and one instrument. Six human serum samples, 5 lithium heparin plasma samples, and controls (rhTSH in Multi-Diluent 15 (MDP 1-5)) were tested in duplicate over twenty days, 2 runs per day, 2 replicates per run with for a total of 40 runs and 80 replicates. Analysis was conducted using ANOVA (Analysis of Variance) and the results are summarized below.

			Repeatability		Within-Laboratory Precision	
Sample	N	Mean µIU/ml (mlU/L)	SD µIU/ml (mlU/L)	CV (%)	SD µIU/ml (mlU/L)	CV (%)
Serum A	80	0.088	0.0022	2.5	0.0032	3.6
Serum B	80	0.196	0.0035	1.8	0.0062	3.1
Serum C	80	0.507	0.0086	1.7	0.0134	2.6
Serum D	80	4.752	0.1083	2.3	0.1293	2.7
Serum E	80	46.749	1.1297	2.4	1.8749	4.0
Serum F	80	97.929	2.1282	2.2	3.4288	3.5
Plasma, lithium heparin A	80	0.099	0.0014	1.4	0.0029	2.9
Plasma, lithium heparin B	80	0.520	0.0089	1.7	0.0175	3.4
Plasma, lithium heparin C	80	4.908	0.0763	1.6	0.1139	2.3

			Repeatability		Within-Laboratory Precision	
Sample	N	Mean µIU/ml (mlU/L)	SD µIU/ml (mlU/L)	CV (%)	SD µIU/ml (mlU/L)	CV (%)
Plasma, lithium heparin D	80	53.262	0.7579	1.4	1.5032	2.8
Plasma, lithium heparin E	80	91.993	3.2754	3.6	5.7348	6.2
Control 1	80	0.104	0.0021	2.1	0.0035	3.4
Control 2	80	0.516	0.0087	1.7	0.0203	3.9
Control 3	80	4.778	0.0811	1.7	0.1316	2.8
Control 4	80	47.494	0.6508	1.4	1.7552	3.7
Control 5	80	99.366	1.5194	1.5	2.9443	3.0

Reproducibility

Six human serum samples, five lithium heparin plasma samples, and controls (MDP 1-5) were tested in replicates of five with one run per day over five days for a total of 225 replicates per sample. Testing was performed using three instruments and three reagent lots. The analysis and results were similar to the repeatability study summarized above.

2. Linearity:

Linearity testing was performed in accordance with CLSI EP06 2nd Edition. The dilution series contained samples spanning 15 concentrations throughout the measuring range. The maximum % deviation from linearity observed was 7.2%. The results of the linearity study support the claimed measuring range of 0.010-150.000 mlU/L.

3. Analytical Specificity/Interference:

Interference:

Interference testing was performed following the recommendations in CLSI EP07 3rd Edition. Human serum specimen pools with native analyte were supplemented with potentially interfering compounds at the levels listed in the table below. The sponsor provided information to support the following claims:

Substances	Concentration tested that demonstrated no significant interference
Hemoglobin	500 mg/dL
Triglycerides	1000 mg/dL
Conjugated bilirubin	40 mg/dL
Unconjugated bilirubin	40 mg/dL
Biotin	0.35 mg/dL
Acetaminophen	15.60 mg/dL
Acetylcysteine	15.00 mg/dL
Acetylsalicylic acid	3.00 mg/dL

Substances	Concentration tested that demonstrated no significant interference
Ampicillin Sodium	7.50 mg/dL
Ascorbic Acid	5.25 mg/dL
Carbimazole	3.00 mg/dL
Cefoxitin	495.00 mg/dL
Cyclosporine	0.18 mg/dL
Doxycycline	1.80 mg/dL
Heparin	7500 units/dL
Ibuprofen	21.90 mg/dL
Levodopa	0.75 mg/dL
Levothyroxine	0.0429 mg/dL
Liothyronine	0.0075 mg/dL
Methimazole	8.00 mg/dL
Methyldopa	2.25 mg/dL
Metronidazole	12.30 mg/dL
Octreotide	0.03 mg/dL
Phenylbutazone	32.10 mg/dL
Propranolol	24.00 mg/dL
Propylthiouracil	30.00 mg/dL
Rifampicin	4.80 mg/dL
Theophylline	6.00 mg/dL
Total Protein	15 g/dL
Cholesterol	400.00 mg/dL
Rheumatoid Factor	00 IU/mL

The sponsor includes the following limitations in their labeling:
Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. This assay is designed to minimize interference from heterophilic antibodies.

Do not use samples that contain fluorescein. Fluorescein levels > 0.24 µg/mL may decrease results in this assay. Evidence suggests that patients undergoing retinal fluorescein angiography can retain amounts of fluorescein in the body for up to 48–72 hours post-treatment. In the cases of patients with renal insufficiency, including many diabetics, retention could be much longer. Such samples can produce falsely depressed values when tested with this assay, and should not be tested. Testing of samples spiked with a theoretical maximum level of fluorescein (250 µg/mL) used in these patients have resulted in TSH levels < 0.06 µIU/mL instead of the true value of 27.99 µIU/mL.

As with any immuno-recognition measurement of a peptide, extremely rare genetic variants may exhibit varying degrees of detection.

Cross-Reactivity Testing:
Cross-reactivity was determined using the candidate device in accordance with CLSI EP07 3rd Edition. Cross-reactivity of samples spiked with various substances did not exceed 5%

at TSH concentrations of approximately 0.400 mIU/L, 5.00 mIU/L, 17.00 mIU/L, and 90.00 mIU/L.

Substance	Concentration Tested (pg/mL)
hCG	200000 mIU/mL
FSH	1500 mIU/mL
LH	600 mIU/mL

High-Dose Hook Effect:
The high-dose hook effect of the candidate device was measured on one instrument using a dilution series. No hook effect was seen up to 3000 µIU/mL. Samples with TSH concentrations above the measuring interval and as high as 3000 µIU/mL will report > 150 mlU/L.

4. Assay Reportable Range:
   See section VII.A.2 Linearity.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
   This assay is traceable to the World Health Organization (WHO) 3rd International Reference Preparation for human TSH (IRP 81/565).

6. Detection Limit:
   Detection capability was determined in accordance with CLSI Document EP17-A2.

   The limit of blank (LoB) was determined to be 0.005 µIU/mL (mIU/L), the limit of detection (LoD) was determined to be 0.008 µIU/mL (mIU/L) and the limit of Quantitation (LoQ) was determined to be 0.010 µIU/mL (mIU/L).

   The LoB corresponds to the highest measurement result likely to be observed for a blank sample with a probability of 95%. The LoD corresponds to the lowest analyte concentration that can be detected with a probability of 95%. The LoQ corresponds to the lowest analyte concentration at which the within laboratory CV is ≤ 20%.

7. Assay Cut-Off:
   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   A total of 404 native human serum samples were assayed using the candidate (y) and predicate (x) devices and the results were analyzed using Passing & Bablok regression. The results from one representative lot are presented below.

N	Sample range		Slope	r	Regression Equation
	Low	High			
404	0.028	147.337	0.948	0.999	y = 0.95x – 0.016 µIU/mL

2. Matrix Comparison:
A matrix comparison study was conducted using matched Serum and Lithium Heparin samples and matched Serum and K2-EDTA samples. The results were analyzed using Passing & Bablok regression. The results are presented below.

Tube (y) vs Serum (x)	Regression Equation	Sample Interval	N	r
Plasma, EDTA	Y=0.99x – 0.019	0.050-147.805 µIU/mL	52	0.999
Plasma, lithium heparin	Y = 1.01x – 0.034	0.115-135.881 µIU/mL	57	0.990

C 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.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The sponsor provided information to support the following claimed expected values reported in the labeling.

Group	N	Reference Interval µIU/mL (mIU/L)
Euthyroid Adults	229	0.55-4.78
Infants (1-23 months)	94	0.87-6.15
Children (2-12 years)	198	0.67-4.16
Adolescents	150	0.48-4.17

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.