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

A. 510(k) Number:

k160541

B. Purpose for Submission:

New device

C. Measurand:

Thyroid Stimulating Hormone (TSH)

D. Type of Test:

Quantitative chemiluminescent immunoassay

E. Applicant:

Sysmex America, Inc.

F. Proprietary and Established Names:

Automated Immunoassay System HISCL-800

HISCL TSH Assay Kit

HISCL TSH Calibrator

HISCL Immuno Multi Control

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)
JIT	Calibrator, secondary	Class II	21 CFR§ 862.1150	Chemistry (75)
JJY	Quality control material (assayed and unassayed)	Class I, reserved	21 CFR §862.1660	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 indication(s) for use below

2. Indication(s) for use:

   The Automated Immunoassay System HISCL-800 is a chemiluminescent chemistry analyzer for the determination of analytes in human serum

   The HISCL TSH assay is a magnetic particle chemiluminescent enzyme immunoassay (CLEIA) for the quantitative determination of TSH levels in human serum using the Automated Immunoassay System HISCL-800. Measurements of thyroid stimulating hormone produced by the anterior pituitary are used in the diagnosis of thyroid or pituitary disorders.

   The HISCL TSH Calibrator is used for calibrating the HISCL TSH Assay kit on the Automated Immunoassay System HISCL-800.

   The HISCL Immuno Multi Control is used for quality control of the HISCL TSH Assay Kit on the Automated Immunoassay System HISCL-800.

3. Special conditions for use statement(s):

   For prescription use

4. Special instrument requirements:

   The Sysmex Automated Immunoassay System HISCL-800

I. Device Description:

HISCL-800 Analyzer:

The HISCL-800 is a fully automated floor model random access immunoassay system that can quantitatively or qualitatively analyze samples for minute traces of a variety of chemistry analytes. The HISCL-800 has a maximum through-put of 100 tests / hour with an analysis time per analyte of 17 minutes and has capacity for 24 on board reagent sets in the cooled reagent storage. Reagent tracking utilizes RFID technology. Using six 5-sample racks, the HISCL-800 has a walk-away capacity for 30 specimens and one STAT sample loading position. An onboard mixer automatically mixes the magnetic particle reagent as needed. The analyzer has a dedicated sample arm which uses disposable tips and three reagent dispensing arms. The HISCL-800 employs chemiluminescent enzyme technology based on CDP-Star™ chemiluminescent substrate. The analyzer has the capacity to run both one-step and two-step sandwich immunoassays.

HISCL TSH Assay Kit

HISCL TSH Assay Kit contains 5 different reagents (R1, R2, R3, R4, and R5), which contain the following ingredients:

R1 reagent (3mL): contains ALP-labeled anti-TSH monoclonal antibodies (mouse) 0.4 U/mL
R2 reagent (3mL): contains streptavidin coated with magnetic particles
R3 reagent (3mL): contains biotinylated anti-TSH monoclonal antibodies (mouse) 9µg/mL
All assay reagents above contain sodium azide as a preservative.

HISCL Substrate Reagent Set

R4 Reagent (40 mL) which also contains sodium azide as a preservative is used for dispersing the magnetic particles before starting the chemiluminescence reaction. The reproducibility of chemiluminescence is improved by dispersing the magnetic particles.

R5 Reagent (70 mL) is analkaline solution with pH 9.6 that contains the chemiluminescent substrate (CDP- Star®): Disodium 2-e-chloro-5-(4-methoxyspiro {1,2-dioxetane-3,2'-(5'-chloro)-tricyclo [3.3.1.13,7] decan}-4-yl)-1-phenyl phosphate 0.48mM

HISCL TSH Calibrators
This calibrator set contains six different levels of calibrator materials, supplied in liquid form (1 mL each). The calibrators contain recombinant TSH.

HISCL TSH C0 (0 µIU/mL)
HISCL TSH C1 (2 µIU/mL)
HISCL TSH C2 (10 µIU/mL)
HISCL TSH C3 (50 µIU/mL)
HISCL TSH C4 (120 µIU/mL)
HISCL TSH C5 (200 µIU/mL)

All calibrators contain sodium azide as a preservative.

HISCL Immuno Multi Control

The HISCL Immuno Multi Control contains two different levels of control materials (level 1 and level 2). HISCL Immuno Multi Controls are lyophilized and are reconstituted using distilled water to 3mL per bottle (3 bottles of each control material are included in each package of the Multi Control).

HISCL Immuno Multi Control Level 1 (targeted at 2.006 µIU/mL)
HISCL Immuno Multi Control Level 2 (targeted at 6.340 µIU/mL)

The HISCL Immuno Mutli controls contain human-derived materials and have been tested and found to be negative for Hepatitis B and HIV 1 and HIV 2 by FDA approved methods.

HISCL Diluent
HISCL Diluent: contains bovine serum albumin
Diluent contain sodium azide as a preservative.

HISCL Probe Washing Solution
HISCL Probe Washing Solution: contains sodium hypochlorite

HISCL Line Washing Solution
HISCL Line Washing Solution: contains Tris-(hydroxymethyl)aminomethane

HISCL Washing Solution
HISCL Washing Solution: contains Tris-(hyroxymethyl)aminomethane

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Siemens ADVIA Centaur XP Immunoassay System
   Siemens ADVIA Centaur XP TSH Assay Kit
   ADVIA Centaur Calibrator B
   Immunoassay Plus Controls

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

   k083844 (for both instrument and TSH assay),
   k920372 (for calibrator)
   k122838 (for control)

3. Comparison with predicate:

   Comparison of the instrument/analyzer:

Similarities and Differences		
Item	Candidate Device Automated Immunoassay System HISCL-800	Predicate Siemens ADVIA Centaur XP Immunoassay System k083844
Intended Use	The Automated Immunoassay System HISCL-800 is a chemiluminescent chemistry analyzer for the determination of analytes in human serum.	Same

Similarities and Differences		
Item	Candidate Device Automated Immunoassay System HISCL-800	Predicate Siemens ADVIA Centaur XP Immunoassay System k083844
System Description	Random access immunoassay system	Same
Throughput	100 tests per hour	Up to 240 tests per hour
Sampler	Universal 5-position rack holds multiple tube types. 6 position rack adapter for sample cups. No pause load and unloading	Universal 5-position rack holds multiple tube types. No pause loading and unloading
Automatic Dilutions	Not available	Available
STAT Handling	An urgent sample is given priority over regular samples. A sample can be placed in the urgent sample holder.	Dedicated STAT port accepts samples any time
Sample Barcodes	EAN/UPC/JAN,ITF, Codabar /NW7,Code39,Code 128	Code 128, Code 39, Codabar, Interleaved 2 of 5
Reagent Cooling	24 position on the reagent disk cooled 2°C to 15°C	30 position reagent tray cooled 4°C to 8°C
Reagent Integrity Control	Tracked using the RFID label ・Reagent item ・Reagent type ・test counts flag ・expired date flag (Lot/onboard)	Barcode reagent identification, automatic inventory tracking and flagging, calibration validity tracked and flagged, reagent on board stability tracked and flagged, reagent expired/reagent low flagging
Reagent Mixing	Automatically mixes the magnetic particle reagent (R2) on board.	ReadyPacks automatically rocked onboard
Monitor	21.5 inch LCD screen Touch panel	19-inch diagonal high-resolution LCD touch screen with adjustable height
Dimensions	Approximately 51.0 (h) X 40.1 (w) X 42.9 (d) in	Approximately 51.5 (h) X 72.4 (w) X 41.0 (d) in
Weight	Approx. 320 kg (704 lbs)	Approx. 545 kg (1200 lbs)

Comparison of the TSH assay:

Similarities and Differences		
Item	Candidate Device HISCL TSH Assay Kit	Predicate Device Siemens ADVIA Centaur XP TSH Assay Kit (k083844)
Intended Use/Indications for use	For the quantitative determination of TSH levels in human serum. Measurements of thyroid stimulating hormone produced by the anterior pituitary are used in the diagnosis of thyroid or pituitary disorders.	Same
Instrument platform	Automated Immunoassay System HISCL-800	ADVIA Centaur XP
Sample Type	Serum	Serum, Heparinized Plasma, EDTA Plasma
Sample Volume	200 µL	Same
Reportable Range	0.008 µIU/mL to 75 µIU/mL	0.008 µIU/mL to 150 µIU/mL

Comparison of the TSH calibrator:

Similarities and Differences		
Item	Candidate Device HISCL TSH Calibrator	Predicate Device ADVIA Centaur Calibrator B (k920372)
Intended Use	The TSH Calibrator is used for calibrating the TSH assay.	Same
Number of Levels	6	2
Form	Liquid	Lyophilized
Matrix	Triethanolamine hydrochloride buffer	Equine serum
Total Target Concentrations	6 different levels: C0, C1, C2, C3, C4 and C5	Low Calibrator High Calibrator

Comparison of the control material:

Similarities and Differences		
Item	Candidate Device HISCL Immuno Multi Control	Predicate Device BioRad Liquichek Immunoassay Plus Controls (k122838)
Intended Use	For quality control of the TSH assay.	Same
Number of Analytes	TSH	Multi-analytes, including TSH
Form	Lyophilized	Liquid
Matrix	Human-derived material	Human serum
Number of Levels	2: Level 1 is targeted to 2.006 TSH Level 2 is targeted to 6.340 TSH	3: Low, Medium and High

K. Standard/Guidance Document Referenced:

CLSI C28-A3c: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory, Approved Guideline -3rd Edition.

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline -3rd Edition.

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

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline - 2nd Edition

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures: Approved Guideline-2nd Edition.

CLSI C56-A: Hemolysis, Icterus, and Lipemia/Turbidity Indices as Indicators of Interference in Clinical Laboratory Analysis; Approved Guideline

CLSI EP25-A: Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.

CLSI I/LA21-A2, Clinical Evaluation of Immunoassays; Approved Guideline - 2nd Edition.

CLSI I/LA30-A, Immunoassay Interference by Endogenous Antibodies; Approved Guideline

L. Test Principle:

The HISCL TSH Assay Kit is an in vitro diagnostic device that measures TSH based on the chemiluminescent enzyme immunoassay method with CDP-Star™ chemiluminescent substrate. The assay utilizes a 1-step sandwich immunoassay, as follows:

1. ALP (alkaline phosphatase)-labeled anti-TSH monoclonal antibodies (mouse) in R1 reagent specifically react with TSH in the sample.

2. Biotinylated anti-TSH monoclonal antibodies (mouse) in R3 reagent specifically bind to TSH, and bind to streptavidin-coated MP (magnetic particles) in R2 reagent.

3. After bound/free (B/F) separation, ALP on MP decomposes CDP-Star ™ substrate in R5 to an excited intermediate, which produces a luminescent signal.

Because the light production increases in proportion to TSH concentration, sample TSH concentration can be obtained with a calibration curve prepared with calibrators.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The five samples (2 controls and 3 serum samples) were each assayed over 20 days, in duplicate, two runs per day, for a total of 80 results per sample. Testing was performed using multiple lots of reagents with multiple instruments. All lots of reagents yielded similar results and one representative lot of reagent is summarized below.

Precision Results Summary: (n=80)

Sample ID	Mean (µIU/mL)	Repeatability (Within-run)		Between-Run Precision		Between-Day Precision		Within-Laboratory Precision	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	1.984	0.045	2.3%	0.020	1.0%	0.021	1.1%	0.054	2.7%
Control 2	5.991	0.122	2.0%	0.088	1.5%	0.069	1.2%	0.165	2.8%
Sample 1	5.044	0.122	2.4%	0.040	0.8%	0.046	0.9%	0.137	2.7%
Sample 2	0.138	0.003	2.2%	0.000	0.0%	0.002	1.4%	0.004	2.9%
Sample 3	23.260	0.461	2.0%	0.193	0.8%	0.447	1.9%	0.670	2.9%

b. *Linearity:*

A contrived high serum sample was mixed with a low contrived sample to create 33 intermediate samples with concentrations that are known relative to one another. The samples (total of 35) tested in this study ranged from 0.001 to 257.887 µIU/mL. The percent deviation from the expected results was ≤ 10% for all concentrations tested. The expected values were plotted against the observed values and the following regression equation was obtained:

$Y = 0.994x + 8.115x10^{-5}$, $R^2 = 1.000$

The sponsor states the data support the claimed measuring range of 0.008-75 µIU/mL for the TSH assay.

High Dose Hook Effect

Five high concentration TSH samples (approximately 2,000 µIU/mL) were prepared. From each sample, three 5-fold serial dilutions were created with the HISCL Diluent to achieve the following TSH levels: 400 µIU/mL, 80 µIU/mL, and 16 µIU/mL. Each serial dilution, plus the neat, high sample, was assayed in triplicate. No hook effect was observed at TSH concentrations up to 2,000 µIU/mL.

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

Traceability:

The HISCL TSH calibrators are traceable to the reference material: WHO Standard 80/558.

Value Assignment:

The HISCL TSH Calibrators contain six different levels of calibrator materials, supplied in liquid form (1 mL each). Primary standards/calibrators are prepared from the WHO Standard 80/558 material and used to assign the values of the initial HISCL TSH standard calibrators which are compared to pre-set specifications for each calibrator concentration. Product (commercial) calibrators are value assigned using the secondary standard calibrators using a similar value assignment process based on an internal procedure. Below are the target values of the calibrators.

HISCL TSH C0 (0 µIU/mL)

HISCL TSH C1 (2 µIU/mL)

HISCL TSH C2 (10 µIU/mL)

HISCL TSH C3 (50 µIU/mL)

HISCL TSH C4 (120 µIU/mL)

HISCL TSH C5 (200 µIU/mL)

The HISCL Immuno Multi controls contain two different levels of control materials, supplied in lyophilized forms. The HISCL Immuno Multi controls are value assigned using the HISCL TSH second standard calibrators. The acceptable range included on the labeling is ± 20% of the targeted value. Below are the target concentrations and ranges of the controls.

HISCL Immuno Multi Control Level 1 (targeted at 2.006 µIU/mL)

HISCL Immuno Multi Control Level 2 (targeted at 6.340 µIU/mL)

Commercial controls should also be used to supplement quality control testing to extend the portion of the measuring range monitored.

Stability of Calibrators and Controls:

Real Time shelf life stability testing of the HISCL TSH Calibrators and HISCL Immuno Multi Controls is on-going. The shelf-life stability studies protocols and acceptance criteria were reviewed and found to be acceptable to support the following claim of 12 months stability at 2-8°C.

Open Vial Stability Testing:

Real-time stability testing of the HISCL TSH Calibrators and HISCL Immuno Multi Controls is ongoing. The open-vial stability studies protocols and acceptance criteria were reviewed and found to be acceptable to support the following claims:

Calibrators: Stable after opening for 60 days at 2-8°C

Controls: Stable after opening for 8 hours at 8-30°C, 7 days at 2-8°C and 60 days at -20°C.

d. Detection limit:

LoB:

Four zero TSH samples were used from four distinct lots of HISCL Diluent as the blank samples in this study. The samples were assayed in replicates of five over four days (n = 80) with each of two lots of test kits on two different instruments (total of four combinations). LoB (for each lot/instrument combination) were calculated according to CLSI EP17-A2. The LoB was determined to be 0.0007µIU/mL.

LoD:

Five low samples were prepared by adding varying amounts of TSH to the diluent so that the values ranged from the LoB (1x), to five-times (5x) the LoB. Each sample was assayed by each of two reagent lots and one instrument (two combinations) 8x/day for five days (n = 40/sample with each lot/instrument combination). From this testing, the standard deviations for the low samples were calculated per the CLSI EP17-A2 formula where: LoD = LoB + 1.645 x standard deviation (SD) of the low sample. The data set with the highest LoD was used to describe the test system. The LoD was determined to be 0.001 µIU/mL.

LoQ (Functional Sensitivity):

LoQ was determined by testing 7 low TSH samples. Four of the samples were human pools where 10 discrete, native serum samples were combined, and TSH was stripped using anti-TSH antibody coated magnetic particles; the three remaining samples were serial dilutions of TSH low control material. The samples were tested twice a day for 20 days (n = 40 results per level), and means, standard deviations, and %CVs were calculated. The TSH concentrations where %CVs did not exceed 20% across the four combinations of reagents and calibrators were: 0.0010, 0.0013, 0.0014, and 0.0014 µIU/mL, respectively. The LoQ/functional sensitivity was determined to be 0.002µIU/mL, which is the lowest concentration at which the total imprecision for the assay does not exceed 20%CV.

The sponsor claims that the assay has a measuring range of 0.008µIU/mL to 75 µIU/mL TSH.

e. *Analytical specificity:*

Interference Testing:

Two serum samples with low and high TSH levels targeted at 0.3µIU/mL and 8µIU/mL, respectively, were used in the study. Moderate and high levels of various biological and pharmaceutical substances as described in the table below were added to the neat samples, and all samples were tested in triplicate. The testing was done with two lots of reagents, one instrument, and one operator. The means were calculated for each sample with and without potential interferents, and the percent differences were calculated. Significant interference was defined as a difference of greater than 10%. No samples demonstrated significant interference at the concentrations noted in the table below.

Interfering Substances Tested

Substance	**Levels Tested**
Hemoglobin	200 mg/dL and 500 mg/dL
Unconjugated bilirubin	20 mg/dL and 40 mg/dL
Conjugated bilirubin	20 mg/dL and 40 mg/dL
Rheumatoid Factor	250 IU/mL and 500 IU/mL
Total protein	6 g/dL and 12 g/dL
Triglycerides	375 mg/dL and 750 mg/dL
Biotin	5 ng/mL and 10 ng/mL
Acetaminophen	10 mg/dL and 20 mg/dL
Ibuprofen	25 mg/dL and 50 mg/dL
Aspirin	33 mg/dL and 65 mg/dL

HAMA:

Two serum samples with low and high TSH levels targeted at 0.3µIU/mL and 8µIU/mL, respectively, were used in the study. HAMA (human anti-mouse antibody) containing serum samples were added to the neat samples to a final concentration of up to 138 ng/mL of HAMA and all samples were tested in triplicate. The differences and percent differences of the means between samples with and without HAMA were calculated. Interference was defined as a difference of greater than 10% in results from spiked samples compared to the expected TSH values of those samples. No significant interference above the pre-defined limit was observed.

Cross Reactivity Study:

Two serum samples with low and high TSH levels targeted at 0.3µIU/mL and 8µIU/mL, respectively, were used in the study. High levels of hCG, FSH, and LH were added to the neat samples, and all samples were tested in triplicate. The differences and percent differences between samples with potential interferents and without potential interferents were calculated. The testing was done with two lots of reagents, one instrument, and one operator. Representative data is shown below:

Sample TSH Concentration measured (Containing cross-reactant) (µIU/mL)	Reference TSH Concentration (No cross-reactant) (µIU/mL)	Interferent	Material added (mIU/mL)	%Cross Reactivity
0.298	0.299	hCG	300,000	-3.33×10^{-10}
0.301	0.299	FSH	1,000	2.00×10^{-7}
0.305	0.299	LH	1,000	6.00×10^{-7}
7.427	7.091	hCG	300,000	1.12×10^{-7}
7.297	7.091	FSH	1,000	2.06×10^{-5}
7.422	7.091	LH	1,000	3.31×10^{-5}

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

One hundred sixty five serum (native) specimens were tested using the candidate device on the Sysmex Automated Immunoassay System HISCL-800 and the ADVIA Centaur TSH assay (predicate device). Testing was performed at an external site over 15 separate days.

A Weighted Deming Regression analysis was performed. The results are summarized in the table below.

N	Sample Range (µIU/mL)	Slope (95% CI)	Intercept (95% CI)	r
165	0.009 -74.604	0.950 (0.936-0.964)	-0.002 (-0.006-0.002)	0.993 (0.991 to 0.995)

b. Matrix comparison:

Not Applicable

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:

   For Reference Range Study:

   One hundred forty-nine prospectively collected serum specimens obtained from presumed apparently healthy individuals (self-reported), between the age of 21 and 70 years, with no personal or family history of thyroid dysfunction, no known thyroid disease, who were not pregnant, not ill, and not taking thyroid medications, were collected and tested. Each specimen was tested for normal values of TSH, FT4, TPOAb and TgAb in order to confirm eligibility. Of the 149 prospectively enrolled subjects, 127 eligible prospectively enrolled subjects, 65 males and 62 females, were included in the data analysis. The specimens were collected from subjects who lived in different areas of the U.S. such that they were representative of the diverse U.S. population.

   The sponsor established the HISCL TSH adult serum reference range of 0.446 μIU/mL to 4.780 μIU/mL using the central 95% interval of their results from this study (2.5^{th}- 97.5^{th} percentile results).

N. Instrument Name:

Automated Immunoassay System HISCL-800

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 entry

4. Specimen Sampling and Handling:

   Automated sample handling

5. Calibration:

   The sponsor states each calibration is valid for 30 days.

6. Quality Control:

   The sponsor recommends performing quality control testing at least once each day.

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

A carry over study has been performed and found to be acceptable.

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.