510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K243570

B Applicant

Siemens Healthcare Diagnostics

C Proprietary and Established Names

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL);
Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L)

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
CEC	Class II	21 CFR 862.1695 - Free thyroxine test system	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modified Device

B Measurand:

Thyroid Stimulating Hormone (TSH)
Free Thyroxine (FT4)

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:

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):

The TSHL method is an in vitro diagnostic test for the quantitative measurement of Thyroid Stimulating Hormone (TSH, thyrotropin) in human serum and plasma on the Dimension® EXL™ integrated chemistry system with LOCI® Module. Measurements of TSH are used in the diagnosis and monitoring of thyroid disease.

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):

The FT4L method is an in vitro diagnostic test for the quantitative measurement of Free Thyroxine in human serum and plasma on the Dimension® EXL™ integrated chemistry system with LOCI® Module. Measurements of free thyroxine are used in the diagnosis and monitoring of thyroid disease.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Dimension® EXL™ with LM System

IV Device/System Characteristics:

A Device Description:

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL)
The Dimension® LOCI® TSHL Flex® reagent cartridge is an in vitro diagnostic device that consists of prepackaged liquid reagents in a plastic eight-well cartridge. The device contains the following reagents: liquid biotinylated TSH antibody (mouse monoclonal), liquid TSH antibody coated Chemibeads (mouse monoclonal), and liquid Streptavidin Sensibeads (Recombinant *E. coli*).

Other materials required to run the assay, but not provided include: LOCI Thyroid Calibrator, MULTI 2 Sample Diluent, TSH Sample Diluent, HM Reaction vessels, Quality Control Materials

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L)
The Dimension® LOCI® FT4L Flex® reagent cartridge is an in vitro diagnostic device that consists of prepackaged liquid reagents in a plastic eight-well cartridge. The device contains the following reagents: liquid Streptavidin Sensibeads (Recombinant *E. coli*), liquid T3 Chemibeads, and liquid FT4 biotinylated antibody (mouse monoclonal).

Other materials required to run the assay, but not provided include: LOCI Thyroid Calibrator, Reagent grade water (for use as Level 1 Calibrator), HM reaction vessels, Quality Control Materials

B Principle of Operation:

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL)
The Dimension® LOCI® TSHL Flex® reagent cartridge is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and a biotinylated anti-TSH monoclonal fragment. The first bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye. The second bead reagent (Chemibeads) is coated with anti-TSH monoclonal antibody and contains chemiluminescent dye. Twelve (12) µL of sample is incubated with biotinylated antibody and Chemibeads to form bead-TSH-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the TSH concentration in the sample.

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L)
The Dimension® LOCI® FT4L Flex® reagent cartridge is a homogeneous, sequential, chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and a biotinylated anti-T4 mouse monoclonal antibody. The first bead reagent (Chemibeads) is coated with triiodothyronine (T3), a naturally occurring, weaker binding analog of T4, and contains chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains a photosensitizer dye. Ten (10) µL of sample is incubated with biotinylated antibody which allows T4 from the sample to saturate a fraction of the biotinylated antibody that is directly related to the free thyroxine (FT4) concentration. In a second step, T3 Chemibeads are added and form bead/biotinylated antibody immunocomplexes with the non-saturated fraction of the biotinylated antibody. Sensibeads are then added and bind to the biotin to form bead pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is an inverse function of the FT4 concentration in the sample.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Dimension® TSHL Flex® reagent cartridge, Dimension® FT4L Flex® reagent cartridge

B Predicate 510(k) Number(s):

K081074, K073604

C Comparison with Predicate(s):

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):

Device & Predicate Device(s):	K243570	K081074
Device Trade Name	Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL)	Dimension® TSHL Flex® reagent cartridge
General Device Characteristic Similarities		
Intended Use/Indications For Use	The TSHL method is an in vitro diagnostic test for the quantitative measurement of Thyroid Stimulating Hormone (TSH, thyrotropin) in human serum and plasma. Measurements of TSH are used in the diagnosis and monitoring of thyroid disease.	Same
Instrument	Dimension® EXL™ with LM system	Same
Analytical Measuring Interval	0.007 – 100 µIU/mL	Same
Adult Reference Intervals	0.358 – 3.74 µIU/mL	Same
Pediatric Reference Ranges	Infant (01 – 23 months): 0.867 – 6.43 µIU/mL Children (02 – 12 years): 0.704 – 4.01 µIU/mL Adolescents (13 – 20 years): 0.516 – 4.13 µIU/mL	Same

Device & Predicate Device(s):	K243570	K081074
General Device Characteristic Differences		
Biotin Interference	≤10% bias in the presence of 1200 ng/mL Biotin	≤10% bias in the presence of 250 ng/mL Biotin

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):

Device & Predicate Device(s):	K243570	K073604
Device Trade Name	Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L)	Dimension® FT4L Flex® reagent cartridge
General Device Characteristic Similarities		
Intended Use/Indications For Use	The FT4L method is an in vitro diagnostic test for the quantitative measurement of Free Thyroxine in human serum and plasma. Measurements of free thyroxine are used in the diagnosis and monitoring of thyroid disease.	Same
Instrument	Dimension® EXL™ with LM system	Same
Analytical Measuring Interval	0.1 – 8.0 ng/dL	Same
Adult Reference Intervals	0.76 – 1.46 ng/dL	Same
Pediatric Reference Intervals	Infant (01 – 23 months): 0.93 – 1.45 ng/dL Children (02 – 12 years):	Same

Device & Predicate Device(s):	K243570	K073604
	0.82 – 1.40 ng/dL Adolescents (13 – 20 years): 0.78 – 1.34 ng/dL	
General Device Characteristic Differences		
Biotin Interference	≤10% bias in the presence of 1200 ng/mL Biotin	≤10% bias in the presence of 100 ng/mL Biotin

VI Standards/Guidance Documents Referenced:

- CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline- Third Edition
- CLSI EP06 2nd Edition: Evaluation of Linearity of Quantitative Measurement Procedures
- CLSI EP07 3rd Edition: Interference Testing in Clinical Chemistry
- CLSI EP09c 3rd Edition: Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline Second Edition
- CLSI EP28-A3c: Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline- Third Edition
- CLSI EP34 1st Edition: Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Repeatability and Within-laboratory
Repeatability and within-laboratory precision were evaluated in accordance with CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline-Third Edition. These studies were run on one Dimension® EXL™ with LM system using three reagent lots.

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
Five serum sample pools were assayed for this study. Each sample was assayed in two (2) replicates per run, with two (2) runs per day separated by a minimum of 2 hours between runs, for 20 days, yielding a total of 40 runs and N = 80 replicates. Results from multiple lots were similar. The results from one representative lot are provided in the table below:

Serum Sample	N	Mean (µIU/mL)	Repeatability		Within-Lab	
			SD (µIU/mL)	%CV	SD (µIU/mL)	%CV
1	80	0.110	0.0029	2.6	0.0040	3.6
2	80	0.372	0.0069	1.9	0.0116	3.1
3	80	3.765	0.0802	2.1	0.1209	3.2
4	80	15.208	0.3108	2.0	0.3936	2.6
5	80	88.676	2.6218	3.0	3.9406	4.4

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):
Three serum samples were assayed in this study. Sample 1 was prepared from a single native sample diluted with T4-stripped human serum, Sample 2 was prepared from a single native serum, and Sample 3 was prepared from pooled native serum. Each sample was assayed in two (2) replicates per run, with two (2) runs per day separated by a minimum of 2 hours between runs, for 20 days, yielding a total of 40 runs and N = 80 replicates. Results from multiple lots were similar. The results from one representative lot are provided in the table below.

Serum Sample	N	Mean (ng/dL)	Repeatability		Within-Lab	
			SD (ng/dL)	%CV	SD (ng/dL)	%CV
1	80	0.81	0.009	1.1	0.021	2.6
2	80	1.50	0.014	0.9	0.033	2.2
3	80	6.41	0.055	0.9	0.168	2.6

Reproducibility
Reproducibility was assessed based on CLSI EP05-A3. These studies were conducted across three Dimension® EXL™ with LM system using three reagent lots, five replicates per day over five days.

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
Five (5) serum samples were assayed. Samples were prepared from pooled native serum or stripped human serum to achieve the target concentrations. The following data represents a summary of all three reagent lots.

Sample	N	Mean (µIU/mL)	Repeatability		Between-Day		Between-Lot	
			SD (µIU/mL)	CV (%)	SD (µIU/mL)	CV (%)	SD (µIU/mL)	CV (%)
Sample 1	225	0.094	0.0025	2.7	0.0049	5.2	0.0022	2.3
Sample 2	225	0.358	0.0088	2.5	0.0089	2.5	0.0051	1.4
Sample 3	225	3.855	0.1082	2.8	0.1193	3.1	0.0000	0.0
Sample 4	225	14.425	0.3358	2.3	0.4980	3.5	0.0117	0.1
Sample 5	225	81.372	2.4293	3.0	2.8811	3.5	1.1456	1.4

Sample	N	Mean (µIU/mL)	Between-System		Reproducibility	
			SD (µIU/mL)	CV (%)	SD (µIU/mL)	CV (%)
Sample 1	225	0.094	0.0040	4.3	0.0071	7.6
Sample 2	225	0.358	0.0163	4.6	0.0211	5.9
Sample 3	225	3.855	0.0755	2.0	0.1778	4.6
Sample 4	225	14.425	0.3037	2.1	0.6732	4.7
Sample 5	225	81.372	0.0000	0.0	3.9389	4.8

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):
Three (3) serum samples were assayed. Samples were prepared from pooled native and stripped human serum to achieve the target concentrations. The following data represents a summary of all three reagent lots.

Sample	N	Mean (ng/dL)	Repeatability		Between-Day		Between-Lot	
			SD (ng/dL)	CV (%)	SD (ng/dL)	CV (%)	SD (ng/dL)	CV (%)
Sample 1	225	0.70	0.008	1.1	0.013	1.9	0.002	0.3
Sample 2	225	1.49	0.014	0.9	0.019	1.3	0.005	0.3
Sample 3	225	6.49	0.058	0.9	0.103	1.6	0.000	0.0

Sample	N	Mean (ng/dL)	Between-System		Reproducibility	
			SD (ng/dL)	CV (%)	SD (ng/dL)	CV (%)
Sample 1	225	0.70	0.008	1.1	0.017	2.4
Sample 2	225	1.49	0.028	1.9	0.036	2.4
Sample 3	225	6.49	0.009	0.1	0.119	1.8

2. Linearity:

Studies were performed with one reagent lot in accordance with CLSI EP06-ED2: Evaluation of the Linearity of Quantitative Measurement Procedures.

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
The dilution series composed of 12 levels (from 0.005 to 101.775 µIU/mL) was prepared by mixing low and high serum pools. All dilutions were assayed in replicates of five (5) and linearity was evaluated using linear regression model. The deviation from linearity did not exceed +/-3% for samples within the assay measuring interval. The results of the linearity study support the claimed analytical measuring interval of 0.007 – 100 µIU/mL (mIU/L).

Dimension® LOCI® Free Thyroxine Hormone Flex® reagent cartridge (FT4L)**:**
The dilution series composed of 10 levels (from 0.00 to 8.41 ng/dL) was prepared by mixing low and high serum pools. All dilutions were assayed in replicates of five (5) and linearity

was evaluated using linear regression model. The deviation from linearity did not exceed +/- 10% for samples within the assay measuring interval. The results of the linearity study support the claimed analytical measuring interval of 0.1 – 8.0 ng/dL.

Dilution Recovery:
Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
A dilution recovery study was conducted to support the claim that samples with TSH concentrations above 100 µIU/mL can be manually diluted 1:5. The study results support that samples with TSH concentrations above 100 µIU/mL may be diluted following the instructions for use. Manual dilution of 5x increases the upper end of the measuring interval from 100 µIU/mL to 500 µIU/mL.

3. Analytical Specificity/Interference:

Endogenous Interference
Interferents were spiked into samples with TSH concentrations of 0.300 µIU/mL or 8.00 µIU/mL. The samples were assayed, and the TSH concentrations of the spiked samples were compared to control samples. No significant interference was defined as less than 10% difference between the mean of control and spiked samples. The substances and the highest concentration tested which did not cause significant interference are listed below.

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):

Potential Interfering Substance	Highest concentration tested at which no significant interference is observed
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	60 mg/dL
Biotin	1200 ng/mL
Hemoglobin	500 mg/dL
Lipemia	3000 mg/dL

The Dimension® LOCI® TSHL Flex® reagent cartridge labeling contains the following limitations:
"Specimens that contain biotin at a concentration of 1200 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to falsely depressed results for patient samples. The recommended adult daily dietary intake for biotin is 30 µg/day. Over the counter dietary supplements promoted for use in hair, skin and nail health may contain 5–100 mg of biotin, with recommendations to take multiple pills per day. Pharmacokinetic studies in healthy adults have shown that, in subjects ingesting 5 mg, 10 mg, and 20 mg of biotin, serum concentrations of biotin can reach up to 73 ng/mL, 141 ng/mL, and 355 ng/mL, respectively. Subjects who take up to 300 mg of biotin per day may have plasma biotin levels as high as 1160 ng/mL"

"Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. This assay has been designed to minimize interference from heterophilic antibodies. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed. As with any immuno-recognition measurement of a peptide, extremely rare genetic variants may exhibit varying

degrees of detection. Thyroid hormone autoantibodies in human serum may interfere with the assay. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution."

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):

Potential Interfering Substance	Highest concentration tested at which no significant interference is observed
Bilirubin (conjugated)	26 mg/dL
Bilirubin (unconjugated)	30 mg/dL
Biotin	1200 ng/mL
Hemoglobin	750 mg/dL
Lipemia	3000 mg/dL

The Dimension® LOCI® FT4L Flex® reagent cartridge labeling contains the following limitations:
"Specimens that contain biotin at a concentration of 1200 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to falsely depressed results for patient samples. The recommended adult daily dietary intake for biotin is 30 µg/day. Over the counter dietary supplements promoted for use in hair, skin and nail health may contain 5–100 mg of biotin, with recommendations to take multiple pills per day. Pharmacokinetic studies in healthy adults have shown that, in subjects ingesting 5 mg, 10 mg, and 20 mg of biotin, serum concentrations of biotin can reach up to 73 ng/mL, 141 ng/mL, and 355 ng/mL, respectively. Subjects who take up to 300 mg of biotin per day may have plasma biotin levels as high as 1160 ng/mL"

"Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. This assay has been designed to minimize interference from heterophilic antibodies. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed. As with any immuno-recognition measurement of a peptide, extremely rare genetic variants may exhibit varying degrees of detection. Thyroid hormone autoantibodies in human serum may interfere with the assay. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution."

Exogenous Interference
See K140842

Cross Reactivity
See K140842

High Dose Hook Effect
Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
The high-dose hook effect of the candidate device was measured on one instrument using a dilution series. No hook effect was observed up to 30,000 µIU/mL TSH.

4. Assay Reportable Range:

   Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
   0.007 – 100 µIU/mL

   Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):
   0.1 – 8.0 ng/dL

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

   Traceability
   Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):
   See K140842

   Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):
   See K140842

6. Detection Limit:
   Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were determined in accordance with CLSI EP17-A2. LoQ was defined as the lowest concentration of analyte with a ≤ 20% CV. The LoB, LoD, and LoQ estimates are summarized below:

	Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL)	Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L)
LoB	0.003 µIU/L	0.03 ng/dL
LoD	0.005 µIU/L	0.05 ng/dL
LoQ	0.007 µIU/L	0.06 ng/dL

7. Assay Cut-Off:
   Not Applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Method comparison studies were conducted with 1 reagent lot in accordance with CLSI EP09C-ED3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples. These studies were performed comparing the candidate device to the comparator method. Two replicates were processed for each sample and the first replicate was analyzed. Slope and Y-intercept and Correlation (r) results were generated using Deming regression.

   Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):

N	Sample Range	Slope	Intercept	Correlation Coefficient (r)
145	0.010-94.387 µIU/mL	0.99	0.039	0.998

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):

N	Sample Range	Slope	Intercept	Correlation Coefficient (r)
146	0.20-7.56 ng/dL	1.02	0.03	0.999

2. Matrix Comparison:

A matrix comparison study was conducted using matched serum and plasma (lithium heparin, sodium heparin, and K2-EDTA) samples. Samples were tested in singlicate. The results were analyzed using Deming regression. The results are presented below.

Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL):

Tube (y) vs Serum (x)	N	Regression Equation	Sample Range	Correlation Coefficient (r)
Plasma, lithium heparin	52	y =1.02x – 0.085	0.012 – 67.283 µIU/mL	0.996
Plasma, sodium heparin	52	y = 1.01x + 0.037	0.012 – 67.283 µIU/mL	0.998
Plasma, EDTA	52	y = 1.00x – 0.010	0.012 – 67.283 µIU/mL	0.998

Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L):

Tube (y) vs Serum (x)	N	Regression Equation	Sample Range	Correlation Coefficient (r)
Plasma, lithium heparin	55	y = 1.00x + 0.02	0.22 – 7.18 ng/dL	1.000
Plasma, sodium heparin	55	y = 1.01x – 0.02	0.22 – 7.18 ng/dL	1.000
Plasma, EDTA	55	y = 1.00x – 0.03	0.22 – 7.18 ng/dL	1.000

The results demonstrate equivalency between serum, lithium heparin plasma, sodium heparin plasma, and EDTA plasma samples for both Dimension® LOCI® Thyroid Stimulating Hormone Flex® reagent cartridge (TSHL) and Dimension® LOCI® Free Thyroxine Flex® reagent cartridge (FT4L).

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:

A study was performed to verify the transference of the Reference Interval established on the currently marketed device (K140842) to the candidate device. The study was performed following CLSI EP28-A3C using serum samples collected from apparently normal human serum donors (minimum of 20). The data from the study supports the transference of the currently marketed device's reference interval to the candidate device.

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.