510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k140842

B. Purpose for Submission:

Adding pediatric reference ranges to previously cleared assays (cleared under k081074 and k130276)

C. Measurand:

Thyroid Stimulating Hormone (TSH)

Free Thyroxine (FT4)

D. Type of Test:

Quantitative, chemiluminescence immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Dimension LOCI Thyroid Stimulating Hormone Flex® reagent cartridge, TSHL

Dimension® LOCI Free Thyroxine Flex® reagent cartridge, FT4L

G. Regulatory Information:

1. Regulation section:

   21 CFR § 862.1690, Thyroid stimulating hormone test system

   21 CFR §862.1695, Free Thyroxine test system

2. Classification:

   Class II

3. Product code:

   JLW

   CEC

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications(s) for use below

2. Indication(s) for use:

   Dimension® 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® 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.

3. Special conditions for use statement(s):

   For prescription use

4. Special instrument requirements:

   Dimension® EXL™ with LM system

I. Device Description:

Dimension® TSHL Cartridge:

The Dimension® 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).

Dimension® FT4L Cartridge:

The Dimension® 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), liquid T3 Chemibeads, and liquid FT4 biotinylated antibody (Mouse monoclonal).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dimension® TSHL Cartridge: Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge

   Dimension® FT4L Cartridge: Dimension® LOCI Free Thyroxine Flex® reagent cartridge

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

   Dimension® TSHL Cartridge: k081074

   Dimension® FT4L Cartridge: k130276

3. Comparison with predicate:

   Dimension® TSHL Cartridge:

Similarities and Differences		
Item	Candidate device	Predicate device Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge (k081074)
Intended 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 on the Dimension® EXL™ integrated chemistry system with LOCI® Module. Measurements of TSH are used in the diagnosis and monitoring of thyroid disease.	Same

Similarities and Differences		
Item	Candidate device	Predicate device Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge (k081074)
Reagents	Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge	Same
Instruments	Dimension® EXL™ with LOCI® Module and Dimension® EXL™ 200	Same
Analytical Measuring Range (Assay Range)	0.007 – 100 µIU/mL	Same
Adult Reference Intervals	0.358 – 3.74 µIU/mL	Same
Pediatric Reference Ranges	Dimension® TSHL Infants (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	None

Dimension® FT4L Cartridge:

Similarities and Differences		
Item	Candidate device	Predicate device Dimension® LOCI Free Thyroxine Flex® reagent cartridge (k130276)
Intended Use	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.	Same

Similarities and Differences		
Item	Candidate device	Predicate device Dimension® LOCI Free Thyroxine Flex® reagent cartridge (k130276)
Reagents	Dimension® LOCI Free Thyroxine Flex® reagent cartridge	Same
Instruments	Dimension® EXL™ with LOCI® Module and Dimension® EXL™ 200	Same
Sample Matrix	Serum, Lithium Heparin Plasma, Sodium Heparin Plasma, EDTA plasma	Same
Analytical Measuring Range (Assay Range)	0.1 – 8.0 ng/dL	Same
Adult Reference Intervals	0.76 – 1.46 ng/dL	Same
Pediatric Reference Ranges	Infants (01 – 23 months) 0.93 - 1.45 ng/dL Children (02 – 12 years) 0.82 - 1.40 ng/dL Adolescents (13 – 20 years) 0.78 - 1.34 ng/dL	None

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

Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline -- Third Edition (CLSI C28-A3c).

L. Test Principle:

Dimension® TSHL Cartridge: The TSH method is a homogeneous, sandwich chemiluminescent immunoassay based on Luminescent Oxygen Channeling Immunoassay (LOCITM) technology. The LOCITM reagents include two latex bead reagents and a biotinylated anti-TSH monoclonal antibody fragment. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. The second bead reagent (Chemibeads) is coated with a second anti-TSH monoclonal antibody and contains chemiluminescent dye. Sample is incubated with biotinylated antibody and Chemibeads to form bead-TSH-biotinylated antibody sandwiches. Sensibeads are added to 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 a direct function of the TSH concentration in the sample.

Dimension® FT4L Cartridge: The FT4L method 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. In a first step, 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 nonsaturated 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Provided in k060090 and k130276.

   b. Linearity/assay reportable range:

   Provided in k060090 and k130276.

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

   Provided in k060090 and k130276.

   d. Detection limit:

   Provided in k060090 and k130276.

   e. Analytical specificity:

   Provided in k060090 and k130276.

   f. Assay cut-off:

   Provided in k060090 and k130276.

2. Comparison studies:

   a. Method comparison with predicate device:

Provided in k060090 and k130276.

b. Matrix comparison:

Provided in k060090 and k130276.

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:

Dimension® TSHL Cartridge: Serum samples were collected at 8 US sites to be representative of the US population diversity. Data from a total of 407 patients (75 infants, 185 children, and 147 adolescents) on one Dimension EXL with Loci Module (LM) instrument and two lots of cartridges were analyzed to establish the Dimension® TSHL assay reference ranges for the studied pediatric population. Results from the 2.5^{th} to 97.5^{th} percentile were used as the pediatric reference ranges. The reference interval for the infant group was calculated by performing a log-transformation of the raw data followed by the application of the robust symmetric method to the transformed data. This approach was selected to be most appropriate for the smaller sample size as the data from this population was highly skewed to the right and a transformation was necessary to obtain a normal distribution. The sponsor has added language to their package insert explaining the uncertainty in the value for the upper limit of the reference range. A non-parametric approach was used to establish the reference intervals for children and adolescents.

Age Range	Reference Ranges
Infants (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

Confidence intervals for the limits of the infant reference range are as follows:

	Lower Limit of reference range	Upper Limit of reference range
90% confidence intervals:	0.710 – 1.04 µIU/mL	5.40 – 7.54 µIU/mL

Dimension® FT4L Cartridge: Serum samples were collected at 8 US sites to be representative of the US population diversity. Data from a total of 411 patients (77 infants, 187 children, and 147 adolescents) one Dimension EXL instrument with LM and two lots of cartridges were analyzed to establish the Dimension® FT4L assay reference ranges for the studied pediatric population. Results from the 2.5th to 97.5th percentile were used as the pediatric reference range.

The reference interval for the infant group was calculated using the robust symmetric method to accommodate the smaller sample size of this population. A non-parametric approach was used to establish the reference intervals for children and adolescents.

Age Range	Reference Ranges
Infants (01 – 23 months)	0.93 - 1.45 ng/dL
Children (02 – 12 years)	0.82 - 1.40 ng/dL
Adolescents (13 – 20 years)	0.78 - 1.34 ng/dL

Confidence intervals for the limits of the infant reference range are as follows:

	Lower Limit of reference range	Upper Limit of reference range
90% confidence intervals:	0.89 – 0.97 ng/dL	1.41 – 1.50 ng/dL

N. Proposed Labeling:

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

O. Conclusion:

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