DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

November 26, 2014

SIEMENS HEALTHCARE DIAGNOSTICS INC.
FRANCES DILLON
SR. MANAGER, REGULATORY AFFAIRS
PO BOX 6101, M/S 514
NEWARK DE 19714-6101

Re: K140842
Trade/Device Name: Dimension® LOCI Free Thyroxine Flex® Reagent Cartridge, FT4L; Dimension® LOCI Thyroid Stimulating Hormone Flex® Reagent Cartridge, TSHL
Regulation Number: 21 CFR 862.1695
Regulation Name: Free thyroxine test system
Regulatory Class: II
Product Code: CEC, JLW
Dated: November 21, 2014
Received: November 24, 2014

Dear Frances Dillon:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the

electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney H. Lias -S

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
*See PRA Statement below.*

510(k) Number *(if known)*
K140842

Device Name
Dimension® LOCI Free Thyroxine Flex® reagent cartridge, FT4L

Indications for Use *(Describe)*
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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

***DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.***

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
*PRAStaff@fda.hhs.gov*

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
*See PRA Statement below.*

510(k) Number *(if known)*
K140842

Device Name
Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge, TSHL

Indications for Use *(Describe)*
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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

***DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.***

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
*PRAStaff@fda.hhs.gov*

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*

SIEMENS

## Section 6. 510(k) Summary of Safety and Effectiveness

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of 21 CFR 807.92 and the Safe Medical Device Act of 1990.

The assigned 510(k) Number is: K140842

## 1. Date Prepared

November 25, 2014

## 2. Applicant Information


*Contact:* Frances A. Dillon
Senior Manager, Regulatory Affairs

*Address:* Siemens Healthcare Diagnostics Inc.
P.O. Box 6101, M/S 514
Newark, DE 19714

*Phone:* 302-631-6951

*Fax:* 302-631-6299

*Email:* frances.a.dillon@siemens.com


## 3. Regulatory Information

**Table 1. Regulatory Information for Dimension® FT4L and TSHL Assays**

| | FT4L | TSHL |
|---|---|---|
| **Trade Name** | Dimension® LOCI Free Thyroxine Flex® reagent cartridge, FT4L | Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge, TSHL |
| **Model Numbers** | RF610 | RF612 |
| **Common Name** | Radioimmunoassay, free thyroxine | Radioimmunoassay, thyroid stimulating hormone |
| **Classification Name** | Free thyroxine test system | Thyroid stimulating hormone test system |
| **FDA Classification** | Class II | Class II |
| **Review Panel** | Clinical Chemistry | Clinical Chemistry |
| **Product Code** | CEC | JLW |
| **Regulation Number** | 862.1695 | 862.1690 |

## 4. Predicate Device Information

The inclusion of pediatric reference intervals to the labeling (Package Inserts) of the Dimension® FT4L and TSHL assays does not require any other device modifications (i.e. no change to design or manufacturing process). No changes were made to the reagents. Therefore, as shown in the table below, the predicate and subject devices are the same.

**Table 2. Summary of Predicate Devices for Dimension® FT4L and TSHL Assays**

| | FT4L | TSHL |
|---|---|---|
| **Predicate Device** | Dimension® LOCI Free Thyroxine Flex® reagent cartridge, FT4L | Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge, TSHL |
| **Subject Device** | Same (As above) | Same (As above) |
| **Predicate 510(k)** | K130276 | K081074 |

## 5. Substantial Equivalence Information

The following table demonstrates substantial equivalence between the predicate Dimension® thyroid assays (with unmodified labeling) and Dimension® thyroid assays which have modified Instructions for Use (Package Inserts) including pediatric reference intervals.

**Table 3. Summary of Substantial Equivalence for Dimension® FT4L and TSHL Assays**

| Item | Predicate Device (Unmodified Labeling) | Subject Device (With Pediatric Reference Intervals) |
|---|---|---|
| **Analytes** | Dimension® FT4L<br>Free Thyroxine (FT4)<br>Dimension® TSHL<br>Thyroid Stimulating Hormone | Dimension® FT4L<br>Same<br>Dimension® TSHL<br>Same |
| **Reagents** | Dimension® FT4L<br>Dimension® LOCI Free Thyroxine Flex® reagent cartridge, FT4L<br>Dimension® TSHL<br>Dimension® LOCI Thyroid Stimulating Hormone Flex® reagent cartridge, TSHL | Dimension® FT4L<br>Same<br>Dimension® TSHL<br>Same |
| **Instruments** | Dimension® EXL™ with LOCI® Module and Dimension® EXL™ 200 | Same |
| **Intended Use Statements** | Dimension® FT4L<br>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 | Dimension ® FT4L<br>Same |

**Table 3. Summary of Substantial Equivalence for Dimension® FT4L and TSHL Assays**

| Item | Predicate Device (Unmodified Labeling) | Subject Device (With Pediatric Reference Intervals) |
|---|---|---|
| | thyroid disease.<br><br>Dimension® TSHL<br>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® TSHL<br>same |
| **Analytical Measuring Range (Assay Range)** | Dimension® FT4L<br>0.1 – 8.0 ng/dL [1.3 – 103 pmol/L]<br>Dimension® TSHL<br>0.007 – 100 µIU/mL [mIU/L] | Dimension® FT4L<br>Same<br>Dimension® TSHL<br>Same |
| **Adult Reference Intervals** | Dimension® FT4L<br>0.76 – 1.46 ng/dL [9.8 – 18.8 pmol/L]<br>The reference interval was transferred from that previously determined for the FT4 method on the Dimension Vista® System. It represents the central 95% of results determined non-parametrically from a population of 199 healthy adults (140 males and 59 females, 18 – 59 years of age). The original determination and transference to the FT4L method was done in accordance with CLSI/NCCLS C28-A2.<br>Dimension® TSHL<br>0.358 – 3.74 µIU/mL [mIU/L]<br>The reference interval was transferred from that previously determined for the TSH method on the Dimension Vista® System. It represents the central 95% of results determined non-parametrically from a population of 297 apparently healthy adults (187 males and 110 females, 18 – 65 years of age). The original determination and transference to the TSHL method was done in accordance with CLSI/NCCLS C28-A2. | Dimension® FT4L<br>Same<br>Dimension® TSHL<br>Same |

**Table 3. Summary of Substantial Equivalence for Dimension® FT4L and TSHL Assays**

| Item | Predicate Device (Unmodified Labeling) | Subject Device (With Pediatric Reference Intervals) |
|---|---|---|
| **Pediatric Reference Intervals** | Dimension® FT4L<br>None | Dimension® FT4L<br>Infants (01 – 23 months)<br>0.93 - 1.45 ng/dL<br>Children (02 – 12 years)<br>0.82 - 1.40 ng/dL<br>Adolescents (13 – 20 years)<br>0.78 - 1.34 ng/dL |
| | Dimension® TSHL | Dimension® TSHL<br>Infants (01 – 23 months)<br>0.867 – 6.43 µIU/mL<br>Children (02 – 12 years)<br>0.704 - 4.01 µIU/mL<br>Adolescents (13 – 20 years)<br>0.516 - 4.13 µIU/mL |

## 6. Standard/Guidance Document Reference

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

## 7. Pediatric Reference Intervals

Data from a total of 411 patients (77 infants, 187 children, 147 adolescents) were analyzed to establish the Dimension® FT4L assay reference intervals for the studied pediatric population. Data from a total of 407 patients (75 infants, 185 children, 147 adolescents) were analyzed to establish the Dimension® TSHL assay reference intervals for the studied pediatric population. Testing was performed on a Dimension® EXL™ with LM system. These pediatric reference intervals, as well as the previously-established euthyroid adult reference intervals and analytical measuring ranges, are presented below.

**Table 4. Comparison of Pediatric and Adult 95% Reference Intervals**

| | Dimension® FT4L | Dimension® TSHL |
|---|---|---|
| **Infants (01 – 23M)** | 0.93 - 1.45 ng/dL | 0.867 – 6.43 µIU/mL |
| **Children (02 – 12Y)** | 0.82 - 1.40 ng/dL | 0.704 - 4.01 µIU/mL |
| **Adolescents (13 – 20Y)** | 0.78 - 1.34 ng/dL | 0.516 - 4.13 µIU/mL |
| **Euthyroid Adults*** | 0.76 - 1.46 ng/dL | 0.358 - 3.74 µIU/mL |
| **Assay Range*** | 0.1 - 8.0 ng/dL | 0.007 - 100 µIU/mL |

* Information taken from existing Instructions for Use (Package Inserts)

A non-parametric approach was used to establish the reference intervals for children and adolescents where the $2.5^{th}$ and $97.5^{th}$ percentiles of the distribution of values were calculated. Because fewer than 120 patient samples were included for the infant age group, the reference intervals were calculated by using a robust measure of location and spread,

as developed by Horn and Pesce and recommended in CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals.

The robust symmetrical method was used for the Dimension FT4L analysis because the data was normally distributed. The reference interval calculated from the actual data using the robust symmetrical method was confirmed with two simulated reference intervals (nonparametric and robust symmetric). Each simulated reference interval was estimated as the means of the 95% upper and lower bounds from 1000 data sets. In each case, a normal distribution was fitted to the actual results, with either n=120 for the non-parametric analysis, or n=77 for the robust symmetric analysis.

For the Dimension TSHL assay, the sample distribution for infant subjects was highly positively skewed. As permitted by CLSI EP28-A3, the actual results were natural log transformed to produce a well-fitted normal distribution. The infant reference intervals were then calculated using the robust symmetric method on the log transformed data. The reference interval was confirmed with two simulated reference intervals (nonparametric and robust symmetric). Each simulated reference interval was estimated as the means of the 95% upper and lower bounds from 1000 data sets. In each case, a normal distribution was fitted to the actual results, with either n=120 for the non-parametric analysis, or n=75 for the robust symmetric analysis.

The 90% confidence intervals for the Infant 95% Reference Intervals are listed below.

**Table 5. Infant Reference Interval - 90% Confidence Intervals for Upper and Lower Limits**

| Infants (01 – 23M) | Dimension® FT4L | Dimension® TSHL |
|---|---|---|
| Calculation Method | Robust Symmetric | Robust Symmetric After Log Transformed |
| **Reference Interval** | 0.93 - 1.45 ng/dL | 0.867 – 6.43 µIU/mL |
| **90% Confidence Interval of Lower Limit** | 0.89 – 0.97 ng/dL | 0.710 – 1.04 µIU/mL |
| **90% Confidence Interval of Upper Limit** | 1.41 – 1.50 ng/dL | 5.40 – 7.54 µIU/mL |

## 8. Performance Characteristics

The inclusion of pediatric reference intervals in the Instructions for Use (Package Inserts) does not necessitate the collection of additional analytical performance data as no changes were made to the reagents. Therefore, all analytical performance data previously reviewed for the Dimension® FT4L and TSHL assays continue to apply to these assays. All performance data is cross-referenced to the predicate 510(k) submissions for the FT4L and TSHL assays (K130276 and K081074).

Specifically, the following studies are not needed for the purpose of this submission:

- Precision/Reproducibility
- Linearity
- Calibrator/Assay Traceability
- Calibrator/Assay Stability
- Assay Cut-off
- Method Comparison
- Matrix Comparison

- Sensitivity (Detection Limits, LoB, LoD, LoQ)
- Analytical Specificity

## 9. Shelf-Life

The inclusion of pediatric reference intervals in the Instructions for Use (Package Inserts) does not necessitate the collection of additional stability data as no changes were made to the reagents. Therefore, all stability methods, acceptance criteria and data previously reviewed for the Dimension® FT4L and TSHL assays continues to apply to these assays.

Specifically, the following stability studies are not needed for the purpose of this submission:

- Shelf Life Stability
- Onboard Stability
- Open Vial Stability

## 10. Conclusions

The Dimension® FT4L and TSHL assays with pediatric reference intervals are substantially equivalent to the currently marketed Dimension® FT4L and TSHL assays.

No changes were made to the reagents. The inclusion of pediatric reference intervals in the Instructions for Use (Package Inserts) does not require a change in the device design or a change in the manufacturing process.

The addition of pediatric reference intervals for the Dimension® FT4L and TSHL assays is further supported by the following rationale:

1. Testing of pediatric patients is within the established indications for use (i.e. for use in the diagnosis and treatment of thyroid disease), as described in 21 CFR §862.1695 and 21 CFR §862.1690.
2. The newly-established pediatric reference intervals are either within or are above the previously-established reference intervals for euthyroid (normal thyroid) adult populations and they are within the analytical measuring ranges of the Dimension® FT4L and TSHL assays. Therefore, the Dimension® FT4L and TSHL assays have appropriate analytical performance to test pediatric patients.