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

A. 510(k) Number:

k073604

B. Purpose for Submission:

New device

C. Measurand:

Free thyroxine (FT4)

D. Type of Test:

Quantitative automated sequential chemiluminescent immunoassay

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Dimension® FT4L Flex® reagent cartridge
LOCI® Thyroid Calibrator
Dimension® EXL™ with LM clinical chemistry system

G. Regulatory Information:

1. Regulation section:

   21 CFR § 862.1695, free thyroxine

   21 CFR § 862.1150, calibrator

   21 CFR § 862.2160, discrete photometric chemistry analyzer for clinical use

2. Classification:

   Class II, Class I

3. Product code:

   CEC, JIT, JJE

4. Panel:

   Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indication(s) for use below.

2. Indication(s) for 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™ with LM system. Measurements of free thyroxine are used in the diagnosis and monitoring of thyroid disease.

   The LOCI® Thyroid Calibrator is an in vitro diagnostic product for the calibration of the FT4L method on the Dimension® EXL™ with LM system.

   The Dimension® EXL™ with LM system is an in vitro diagnostic device that is intended to measure a variety of analytes in human body fluids. The system utilizes photometric, turbidimetric, chemiluminescence and integrated ion selective multisensor technology for chemical and immunochemical applications for clinical use.

3. Special conditions for use statement(s):

   For prescription use and samples should not be diluted. Patient samples may contain heterophile antibodies that could react to give falsely elevated or depressed results.

4. Special instrument requirements:

   Dimension® EXL™ with LOCI Module (LM) clinical chemistry system

I. Device Description:

The Dimension® FT4L Flex® reagent cartridge consists of prepackaged liquid reagents containing two synthetic beads, and a biotinylated anti-T4 mouse monoclonal antibody in a plastic eight-well cartridge.

The LOCI® Thyroid Calibrator is a liquid, bovine serum albumin based product containing human thyroxine. There are four calibrator levels with target values of 0.8, 1.6, 4.0 and 8.4

ng/dL.

The Dimension EXL with LM system is a floor model, fully automated, microprocessor-controlled, integrated instrument which uses the Dade Behring Flex® reagent cartridge. It is a member of the Dimension® XL family of instruments. The difference between the Dimension® EXL and previous iterations is that it contains a new module for performing chemiluminescent immunoassays. The module is the LOCI module.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dimension Vista® FT4L Flex®
   Dimension Vista® LOCI 1 Cal®
   Dimension® XL Clinical Chemistry System

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

   k944093, k053531

3. Comparison with predicate:

   a. **Dimension® EXL™ with LOCI Module (LM) Clinical Chemistry System**

Similarities		
Item	Device: Dimension® EXL™ with LOCI Module	Predicate: Dimension® RxL Clinical Chemistry System
Intended use	Measures a variety of analytes, including enzyme activities, in body fluids.	Same
System Control	Fully automated and controlled by microprocessors.	Same
User interface	Contains graphical user interface screens.	Same
Detection technologies	Contains a photometer, a heterogeneous module and a multisensor electrode for performing photometric tests, and electrolyte tests.	Same
Reagents	Uses pre-packaged Flex® reagent cartridges. Reagents are hydrated and stored on-board the instrument.	Same
System fluids	Uses the same system fluids which include chemistry wash, reagent probe cleaner and sample probe cleaner. These fluids are stored on-board the instrument.	Same
Temperature	Reagents are stored at 2 - 8°C. The	Same

Similarities		
Item	Device: Dimension® EXL™ with LOCI Module	Predicate: Dimension® RxL Clinical Chemistry System
control	cuvette reaction temperature is approximately 37°C.	

Differences		
Item	Device: Dimension® EXL™ with LOCI Module	Predicate: Dimension®RxL Clinical Chemistry System
Detection technologies	The Dimension® EXL™ with LM system has a LOCI® module for high-sensitivity homogeneous immunoassay tests.	The Dimension® RxL Max® system performs heterogeneous immunoassays and does not have a LOCI® module.
Temperature control	The HM incubation temperature on the Dimension® EXL™ with LM system is approximately 37°C.	The HM incubation temperature on the Dimension® RxL Max® system is approximately 42°C.
Operating System	The Dimension® EXL™ with LM system has a LINUX operating system	The Dimension® RxL Max® has a QNX operating system.

b. **LOCI® Thyroid Calibrator Material**

Similarities		
Item	Device: Dimension® EXL LOCI Calibrator	Predicate: Dimension Vista® LOCI 1 Cal®
Form	Calibrator contains thyroxine in a liquid bovine serum albumin matrix	Same
Traceability	Traceable to a master pool	Traceable to same master pool

Differences		
Item	Device: Dimension® EXL LOCI Calibrator	Predicate: Dimension Vista® LOCI 1 Cal®
Intended use	The LOCI® Thyroid Calibrator is used to calibrate the Dimension FT4L method on the Dimension® EXL™ with LM system.	The Dimension® LOCI 1 Cal is used to calibrate the Dimension® FT4 method on the Dimension® Vista system.
Analyte	The LOCI® Thyroid Calibrator contains Thyroxine.	The Dimension® LOCI® 1 Calibrator contains Thyroxine, TSH and FT3.

Differences		
Item	Device: Dimension® EXL LOCI Calibrator	Predicate: Dimension Vista® LOCI 1 Cal®
Calibrator levels	The LOCI® Thyroid Calibrator kit contains Levels 2 through 5. The target concentrations are 0.8, 1.6, 4.0 and 8.4 ng/dL. The Level 1 Calibrator is deionized water which is supplied by the customer.	The Dimension® LOCI 1 Calibrator kit contains levels B, C, E and F for calibrating the Dimension Vista™ FT4 method.

c. **Dimension® FT4L Flex® reagent cartridge**

Similarities		
Item	Device: Dimension® FT4L Flex®	Predicate: Dimension Vista® FT4L Flex®
Intended Use	In vitro diagnostic use for the quantitative measurement of Free Thyroxine in human serum and plasma.	Same
Assay Range	0.1 - 8.0 ng/dL.	Same.
Sample Type	Human serum and plasma	Same
Technology	LOCI® technology.	Same.
Sample size	Sample volume of 10µL.	Same.
Reagents and antibody	There are three (3) reagents - streptavidin sensibeads, T3 chemibeads and FT4 biotinylated antibody (containing mouse monoclonal antibody).	Same.

Differences		
Item	Device: Dimension® FT4L Flex®	Predicate: Dimension Vista® FT4L Flex®
Intended Use	There are no differences with respect to this attribute.	
Assay Range	There are no differences with respect to this attribute.	
Technology	There are no differences with respect to this attribute.	
Sample size	There are no differences with respect to this attribute.	
Reagents and antibody	There are no differences with respect to this attribute.	

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

CLSI References:

1. CLSI EP6-A Evaluation of Linearity of Quantitative Measurement Procedures: a statistical approach
2. CLSI EP7-A2 A Guideline for Interference Testing in Clinical Chemistry
3. CLSI EP17-A Protocols for Determination of Limits of Detection

FDA Guidance Documents:

1. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
2. Guidance for Industry and FDA Staff ODE
3. Guidance for Off-the-Shelf Software Use in Medical Devices; Final ODE
4. General Principles of Software Validation; Final Guidance for Industry and FDA Staff OC
5. Guidance for Industry - Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software OC
6. Guidance for Industry - Abbreviated 510(k) Submissions for In Vitro Diagnostic Calibrators; Final OIVD
7. Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy OIVD

L. Test Principle:

The FT4L method is a homogenous, 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 T4 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.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

    a. Precision/Reproducibility:

The precision study was conducted using Bio-Rad Lyphochek® commercial controls and serum pools. Serum pool 1 was prepared from normal human serum. Serum pool 2 was prepared from normal human serum spiked with USP grade Thyroxine. The Bio-Rad levels were 0.71, 2.20 and 5.67 ng/mL. The serum pools were 1.17 and 6.36 ng/dL. These concentrations span the measuring range which is 0.1 - 8.0 ng/dL. There were two runs per day for twenty days. Measurements were taken by two operators. The data was collected on one reagent lot on one instrument. The data was analyzed using analysis of variance. The data is summarized below.

			Repeatability			**Within-Lab**		
	Mean		**SD**		**% CV**	**SD**		**%CV**
Material	ng/dL	pmol/L	Ng/dL	pmol/L		ng/dL	pmol/L	
Bio-Rad Lyphochek®, Level 1	0.71	9.2	0.01	0.2	1.78	0.02	0.2	2.66
Bio-Rad Lyphochek®, Level 2	2.20	28.3	0.04	0.5	1.73	0.12	1.6	5.51
Bio-Rad Lyphochek®, Level 3	5.67	73.0	0.08	1.0	1.36	0.28	3.6	4.99
Serum Pool 1	1.17	15.0	0.02	0.2	1.49	0.04	0.6	3.70
Serum Pool 2	6.36	81.8	0.06	0.8	1.01	0.27	3.5	4.23

b. Linearity/assay reportable range:

The measuring range was determined using the Level 5 LOCI® Thyroid Calibrator and the calibrator base matrix. Intermediate levels were prepared by proportional mixing of these calibrators to produce concentrations evenly distributed across the measuring range. There were eleven concentrations (0.15-8.62 ng/dL) evenly distributed across the measuring range. Each sample was assayed in replicates of n=5. The data was analyzed using least squares linear regression. The quadratic term of a second order polynomial fit was statistically insignificant (p value = 0.2911), supporting linearity across the measuring range. The results from least squares linear regression analysis were: slope = 1.03, y-intercept = -0.21 and R^2 = 1.00.

Based on this study and on the Limit of Detection (see section *d* below), the reportable range was determined to be 0.1-8.0 ng/dL. Samples with results higher than 8.0 ng/dL will be reported as greater than 8.0 and the results are flagged by the Dimension® EXL™ with LM system. Samples above the measuring range should not be diluted. This is stated in the instructions for use, in the section "Analytical Measurement Range" of the labeling. The Dimension® FT4L method is not a sandwich immunoassay. Hook effect is not applicable.

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

Calibrator Traceability:

USP-grade thyroxine is spiked into stripped human serum at different concentrations. This becomes the "Anchor Pool". The "Anchor Pool" values are validated in-house.

A Master Pool is developed from stripped bovine albumin to which different concentrations of thyroxine have been added. Values for the Master Pool are derived by multiple analyses against the Anchor Pool calibration curve. LOCI® Thyroid Calibrator value assignment is established by measurement against the Master Pool calibration.

Stability:

The shelf life and opened bottle stability of the LOCI® Thyroid Calibrator is on-going using real-time data collected from three (3) lots of the calibrator. All testing is being performed using product which is in its final container. The target shelf life is 12 months. The target open bottle stability is 3 months.

Closed vial stability protocol:

Identical lots of calibrators are used. One set is stored at 4°C (test) throughout the study and the other at -70°C (control). Both sets of calibrators will be tested at Day 0 and monthly thereafter for 12 months plus a minimum of 6 days. Replicates of each level will be analyzed for acceptable recovery and drift over time. The test lot will be evaluated for recovery against the calibration curve derived from the control lot.

Open vial stability protocol:

Identical lots of calibrators are used. Both sets are stored at 4°C. The control set will be unopened throughout the study and the other stored opened (test). The test calibrator is returned to 2-8°C storage to simulate worst-case usage of opened calibrators. At each time point, the Dimension® FT4L method is calibrated using the control calibrators to generate a standard curve. The test calibrators are recovered from the standard curve. Recovery of the test calibrators versus time is plotted and drift is determined by the slope of the regression line.

d. Detection limit:

A Limit of Detection (LoD) and Limit of Blank (LoB) study was conducted using four blank samples and four low analyte samples. The four blank samples were water, phosphate buffered saline, HEPES buffered saline and stripped serum. The low analyte samples were prepared from four individual patient samples that were diluted with stripped serum to levels that were approximately 4 times the limit of the blank.

Each blank and low analyte sample was assayed in triplicate using two reagent lots on two instruments over three days. The Limit of Blank was determined from the non-parametric distribution of one-hundred-and-forty-four (144) measurements of the blank samples. The Limit of Detection was calculated from the following equation: $LoD = LoB + (C_p \times SD_s)$.

The LoB was determined from non-parametric distribution of 144 blank measurements (95 % interval). The LoD for FT4L is 0.06 ng/dL (0.77 pmol/L) with proportions of false positives (α) and false negatives (β) less than 5%, and a LoB of 0.03 ng/dL (0.39 pmol/L).

= 0.03 ng/dL
LoD = LoB + (Cp x SDs)
= 0.03 ng/dL + (1.648 * 0.0169 ng/dL)
= 0.03 ng/dL + 0.03 ng/dL
= 0.06 ng/dL.
The Limit of Detection was calculated from the following equation: $LoD = LoB + (C_p \times SD_s)$.

e. Analytical specificity:

<u>Analytical Specificity</u>

Analytical specificity was evaluated for the Dimension® FT4L method on the Dimension® EXL™ with LM system. One hundred normal patient samples were assayed in duplicate for albumin, thyroid binding globulin (TBG) and free thyroxine (FT4). The data was analyzed using least squares linear regression. No significant correlation was observed between albumin and FT4 (r=0.042) or between TBG and FT4 (r=0.145). Samples from normal patients were used in the study. The range of values as determined by the Dimension® EXL™ with LM system were:

Free thyroxine values: 0.61 - 1.61 ng/dL.
Albumin values: 3.1 - 8.0 g/dL.
TBG values: 8 - 35 mg/L

Cross reactivity was evaluated against monoiodotyrosine (1 mg/dL), diiodotyrosine (1 mg/dL), d-thyroxine (10 µg/dL), L-Triiodothyronine (600 ng/dL), R-Triiodothyronine (100 ng/dL) and 3,5-Diiodo-L-Thyronine (600 ng/dL). The calibrator base material was used as a control. Test samples were prepared with the cross reactant substance spiked into calibrator base matrix. Samples were assayed in replicates of n=5. Cross reactivity was calculated as the difference between the mean of the test and control sample. The Dimension® FT4L Flex® had cross-reactivity which was equivalent to the predicate device.

Substance	Concentration of substance	Test Sample With substance (ng/dL)	Control Without substance (ng/dL)	Cross reactivity (ng/dL)
Monoiodotyrosine	1 mg/dL	0.20	0.17	< 0.1
Diiodotyrosine	1 mg/dL	0.16	0.17	<0.1
d-Thyroxine	10 µg/dL	4.30	0.17	>4
L-Triiodothyronine	600 ng/dL	0.19	0.17	<0.1
R-Triiodothyronine (rT3)	100 ng/dL	0.20	0.17	<0.1
3,5-Diiodo-L-Thyronine (L-T2)	600 ng/mL	0.19	0.17	<0.1

Endogenous Interference

Potential endogenous interferents were added to two serum pools. Pool 1 contained normal human serum (1.1 ng/dL free thyroxine). Serum pool 2 was prepared from normal human serum spiked with 3 ng/dL USP grade Thyroxine. Samples were assayed in replicates of n=5 and the means calculated.

The control pool consisted of normal human serum with the appropriate amount of buffer added.
The % bias was calculated using the following equation.

$$\% \text{ Bias} = \frac{\text{Test sample} - \text{Control}}{\text{Control}} \times 100$$

Significant interference is defined as a bias exceeding 10%.

Pool 1 (FT4 = 1.1 ng/mL or 14 pg/mL)

Substance	Concentration of Interferent	Bias %
Hemoglobin (hemolysate)	750 mg/dL [0.47 mmol/L]	< 10
Bilirubin (unconjugated)	30 mg/dL [513 µmol/L]	< 10
Bilirubin (conjugated)	26 mg/dL [445 µmol/L]	< 10
Lipemia (Intralipid®)	3,000 mg/dL [33.9 mmol/L]	< 10

Pool 2 (FT4 = 3 ng/mL or 39 pg/mL)

Substance	Concentration of Interferent	Bias %
Hemoglobin (hemolysate)	750 mg/dL [0.47 mmol/L]	< 10
Bilirubin (unconjugated)	30 mg/dL [513 µmol/L]	< 10
Bilirubin (conjugated)	26 mg/dL [445 µmol/L]	< 10
Lipemia (Intralipid®)	3,000 mg/dL [33.9 mmol/L]	< 10

Co-administered Drugs and Physiological Substance Interferences

The following substances caused elevated FT4L results. The % bias is the larger of the two results from testing at free thyroxine concentrations of 1.1 ng/dL and 3 ng/dL.

Dimension® FT4L interfering substances

Substance	Concentration	% Bias
Carbamazepine	3 mg/dL	14%
Diclofenac	50 mic/mL	90%
Furosemide	6 mg/dL	85%
Ibuprofen	50 mg/dL	92%
Linoleic acd	2.8 mg/mL	175%
Mefanamic acid	0.1 mg/mL	106%
Oleic acid	2.8 mg/mL	80%
Phenylbutazone	15 mg/dL	47%
Phenytoin	5 mg/dL	13%
Salicylic acid	60 mic/mL	73%

The following substances did not cause significant interference with the assay, which is defined as % bias < 10%.

Dimension® FT4L non-interfering substances

Substance	Concentration
Acetaminophen	20 mg/dL
Amikacin	8 mg/dL
Amiodarone	6 mic/mL
Ampicillin	5.3 mg/dL
Ascorbic acid	6 mg/dL
Biotin	100 ng/mL
Caffeine	6 mg/dL
Chloramphenicol	5 mg/dL
Chlordiazepoxide	1 mg/dL
Chlorothiazide	20 mic/mL
Chlorpromazine	0.2 mg/dL
Cimetidine	2 mg/dL
Creatinine	30 mg/dL

Dextran 40	6000 mg/dL
Diazepam	0.51 mg/dL
Digoxin	5 ng/mL
Erythromycin	6 mg/dL
Ethanol	400 mg/dL
Ethosuximide	25 mg/dL
Gentamicin	1 mg/dL
Heparin	3 U/mL
Immunoglobulin (IgG)	5 g/dL
Lidocaine	1.2 mg/dL
Lithium	2.2 mg/dL
Methimazole	4 mic/mL
Nicotine	0.1 mg/dL
Penicillin G	25 U/mL
Pentobarbital	8 mg/dL
Phenobarbital	15 mg/dL
Primidone	4 mg/dL
Propxyphene	0.16 mg/dL
Prophlthiouracil	50 mic/mL
Rheumatoid Factor	277 U/mL
Theophylline	4 mg/dL
Urea	500 mg/mL
Uric acid	20 mg/mL
Valproic acid	50 mg/dL

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

180 patient samples were obtained retrospectively from either blood banks or from local hospitals. Samples were frozen at the collection site and tested at the manufacturer's site. The samples were assayed on both the new device and the predicate device on the same day. The range of values for the Dimension® FT4L Flex® on the Dimension® EXL™ with LM was 0.16 - 7.30 ng/dL. The range of values for the Dimension® FT4 Flex® on the Dimension Vista™ was 0.16 - 7.45 ng/dL. The data was analyzed using least squares linear regression. The summary regression statistics and 95% confidence interval are provided below.

Slope = 0.97 (0.96 to 0.97), y-int = -0.03 (-0.05 to -0.01), r = 0.999, Sy,x = 0.08 ng/dL, n = 180

The values span the proposed measuring range of 0.1 - 8.0 ng/dL

b. Matrix comparison:

Serum/plasma studies were performed to characterize the correlation between with sodium heparin, lithium heparin and EDTA plasma. 33 samples were assayed in multiple replicates of each type. Samples ranged from 0.82-7.31 ng/dL. Data was analyzed using least squares linear regression and is summarized below.

Sample Type Comparison	**Slope**	**Intercept**	**Correlation coefficient, r**	**n**
Sodium Heparin vs. Serum	0.96	0.02	0.998	33
Lithium Heparin vs. Serum	1.03	-0.04	1.000	33
EDTA plasma vs. Serum	0.97	-0.03	0.998	33

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. Results above 8.0 ng/mL are to be reported as > 8.0 ng/mL.

5. Expected values/Reference range:

The expected values were transferred from those previously determined on the Vista system using CLSI C28-A2 as a guideline. The values represent the central 95% of

results determined non-parametrically from a population of 199 apparently healthy adults (140 males and 59 females). The following values are provided in the labeling.

0.76-1.46 ng/dL (9.8-18.8 pmol/L)

N. Instrument Name:

Dimension® EXL™ with LOCI Module (LM) Clinical Chemistry System

O. System Descriptions:

1. Modes of Operation:

   The Dimension® EXL™ with LOCI Module (LM) Clinical Chemistry System is a discrete, random access multi-functional analytical device that processes chemical and immunoassay methodologies utilizing photometric, turbidimetric, chemiluminescence, and integrated ion selective multisensor detection technologies.

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 labeled tubes, racks, or sample cups

4. Specimen Sampling and Handling:

   Uncapped direct patient tube sampling is provided via sample racks containing slots for up to ten samples. Barcoded sample cups may also be used. Non-barcoded samples can be manually programmed with unique identifiers and rack position. The racks are loaded onto a sample wheel where a sampling arm picks up a portion of the specimen and delivers it to the appropriate testing vessel or area. The instrument can be programmed to evaluate degree of hemolysis, icteric, and lipemia. It can also be programmed to perform automatic dilutions, reflex testing and repeats.

5. Calibration:

   Automatic and on-demand calibrations can be performed. Calibration calculations are automatically performed using either linear regression or log-logit. Calibration curves and calibration history are stored in the software and can be reviewed for acceptance by the operator.

6. Quality Control:

   Automatic QC processing and alerts are present. QC records are stored on-board the device for 108-270 days, depending on the number of quality control levels are run. Results can be displayed as Levy-Jennings plots. QC statistics can be generated from the stored data.

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

The software documentation was prepared in accordance with the FDA guidance document "Guide for the Content of Premarket Submission for Software Contained in Medical Devices" and demonstrates the Dimension® EXL™ with LM clinical chemistry system was developed under good software lifecycle practices comparable to other medical devices of the same type.

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.