FEB - 2 2009

SUMMARY OF SAFETY AND EFFECTIVENESS

1.1 Assigned 510(k) Number

The assigned 510(k) number is k083373.

1.2 Sponsor Name and Address

Siemens Healthcare Diagnostics (formerly Siemens Medical Solutions Diagnostics)
511 Benedict Avenue
Tarrytown, NY 10591

1.3 Contact

Philip Liu, Ph.D.
Manager, Regulatory Affairs & Compliance
(914) 524-2443
philip.liu@siemens.com

1.4 Device Name

Trade Name:	IMMULITE® 2000 Free T4
Common Name:	Free Thyroxine
Classification:	Class II device CEC 21 CFR 862.1695
Catalog Numbers:	**L2KFT42** (200 tests), **L2KFT43M** (3000 tests), **L2KFT46** (600 tests), **L2KFT46M** (6000 tests)

1.5 Description of Device

The IMMULITE 2000 Free T4 is a solid-phase, enzyme-labeled chemiluminescent competitive immunoassay. The solid phase (bead) is coated with monoclonal murine anti-T4 antibody. The liquid phase consists of alkaline phosphatase (bovine calf intestine) conjugated to T4.

The patient sample and the reagent are incubated together with the coated bead for 30 minutes. During this time, free T4 in the sample competes with enzyme conjugated T4 in the buffer for a limited number of antibody binding sites on the bead. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, the chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

The IMMULITE 2000 Free T4 procedure is a *direct* or *single test* assay, in the sense that its results are not calculated as a function of total T4, but interpolated

from a (stored) standard curve calibrated in terms of free T4 concentrations.[1] In this respect it differs from so-called free T4 index determinations. Unlike the classic equilibrium dialysis methods, it requires neither a pre-incubation step nor preliminary isolation of the free fraction by dialysis or column chromatography.

Incubation Cycles: 1 × 30 minutes
Time to First Result: 35 minutes

1.6 Indications for Use

IMMULITE® 2000 Free T4 assay is intended for use as follows:

> For *in vitro* diagnostic use with the IMMULITE 2000 Systems Analyzers — for the quantitative measurement of non-protein-bound thyroxine (free T4) in serum and heparinized plasma, as an aid in the clinical assessment of thyroid status.

1.7 Manufacturing Site

IMMULITE 2000 Free T4 assay is manufactured at the following locations:

Siemens Healthcare Diagnostics (formerly Siemens Medical Solutions Diagnostics)
5700 West 96th Street
Los Angeles, CA 90045-5597
FDA Establishment #: 2017183

Siemens Healthcare Diagnostics (formerly Siemens Medical Solutions Diagnostics)
5210 Pacific Concourse Drive
Los Angeles, CA 90045-6900
FDA Establishment #: 3005250747

1.8 Comparison to the Predicate

The IMMULITE 2000 Free T4 assay was cleared with the IMMULITE 2000 instrument (k970227) and predicated on the IMMULITE Free T4 assay (k971792). The revised IMMULITE 2000 Free T4 assay, described in this submission, is predicated on the Siemens Healthcare Diagnostics ADVIA Centaur Free T4 (FrT4) assay (k961510/k971418).

A summary of the features of the IMMULITE 2000 Free T4 assay and the predicate device ADVIA Centaur FrT4 is presented below.

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[1] Wosilait WD. A theoretical analysis of the distribution of thyroxine among sites on thyroid binding globulin, thyroid binding prealbumin and serum albumin. Res Commun Chem Pathol Pharmacol 1977;16:541–8.

Performance of the IMMULITE 2000 Free T4 assay was determined in analytical performance validation studies and in method comparison studies comparing the IMMULITE 2000 Free T4 with the predicate device.

	IMMULITE 2000 FREE T4 Immunoassay (Device)	**ADVIA Centaur FrT4 Immunoassay (Predicate)**
Indications for Use	For the quantitative measurement of non-protein-bound thyroxine (free T4) in serum, as an aid in the clinical assessment of thyroid status.	For *in vitro* diagnostic use in the quantitative determination of free thyroxine (Fr T4)
Sample Type (s)	Serum and plasma	Serum
Assay Type	One-cycle immunoassay	One-cycle immunoassay
Cycle1Incubation	Anti-T4 Mab (on ¼" bead) + serum FT4 + T4-Alkaline Phosphatase	Lite reagent (T4- acridinium ester) + serum FT4 + solid phase (anti-T4 Polyclonal antibody on microparticles)
Incubation time	30 minutes	7.5 minutes
Sample Volume	10 uL	25 uL
Reportable range	0.3 – 6.0 ng/dL	0.1 – 12.0 ng/dL
Analytical Sensitivity	LoB = 0.05 ng/dL LoD = 0.13 ng/dL Functional Sensitivity = 0.25 ng/dL	Minimum Detectable Concentration of 0.1 ng/dL
Precision (Total)	10.2%@ 0.51 ng/dL 6.4% @ 1.13 ng/dL 3.6% @ 2.91 ng/dL	6.56%@ 0.47 ng/dL 3.03% @ 1.08 ng/dL 2.73% @ 3.09 ng/dL
Endogenous Interference	No significant interference from conjugated/unconjugated bilirubin (up to 20 mg/dL), hemoglobin (up to 634 mg/dL) or triglycerides (up to 1000 mg/dL).	No significant interference from conjugated bilirubin (up to 20 mg/dL), hemoglobin (up to 300 mg/dL) or triglycerides (up to 1000 mg/dL).
Accuracy / Correlation (Serum)	Y = 1.06x - 0.001 r = 0.981 (vs. ADVIA Centaur FrT4)	Y = 0.99x + 0.02 r = 0.99 (vs. ACS:180 FrT4)

1.9 Expected Results

The expected results for the IMMULITE 2000 Free T4 assay are based on the established ranges of the ADVIA Centaur Free T4 assay (Predicate Device). Ranges for the ADVIA Centaur FrT4 assay were established using serum obtained from 388 apparently healthy individuals. Serum was analyzed with the ACS: 180® FrT4 assay and confirmed for the ADVIA Centaur FrT4 assay by analyzing 283 samples in the range of 0.14 – 11.1 ng/dL (1.81 to 143 pmol/L). Expected results are as follows:

Clinical Condition	FT4 Range (ng/dL)	FT4 Range (pmol/L)
Euthyroid	0.89 – 1.76	11.5 – 22.7
Hypothyroid	less than 0.89	less than 11.5
Hyperthyroid	greater than 1.76	Greater than 22.7

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.

1.10 Reportable Range

The IMMULITE 2000 Free T4 is a quantitative assay with a reportable range from 0.3 to 6 ng/dL (3.9 to 77.2 pmol/L).

1.11 Limit of Blank

The determination of Limit of Blank was guided by Clinical Laboratory Standards Institute (CLSI): *Protocols for Determination of Limits of Detection and Limits of Quantitation*; Approved Guideline. CLSI document EP17-A (ISBN 1-56238-551-8).

This guideline defines Limit of Blank (LoB) as the highest value expected to be seen in a series of results for samples that contain no analyte.

The LoB claim for the IMMULITE 2000 Free T4 is 0.05 ng/dL.

1.12 Limit of Detection

The determination of Limit of Detection was guided by Clinical Laboratory Standard Institute (CLSI): *Protocols for Determination of Limits of Detection and Limits of Quantitation*; Approved Guideline. CLSI document EP17-A (ISBN 1-56238-551-8).

This guideline defines the Limit of Detection (LoD) as the actual concentration at which an observed test result is likely to exceed the Limit of Blank (LoB) and may therefore be declared as detected.

The LoD claim for the IMMULITE 2000 Free T4 is 0.13 ng/dL.

1.13 Functional Sensitivity

The concentration with a 20% coefficient of variation for the IMMULITE 2000 Free T4 is 0.25 ng/dL. This is the functional sensitivity of this assay.

1.14 Linearity/Recovery

Linearity/recovery was evaluated by assaying as unknowns the calibrators and calibrators mixed 1:1 to create intermediate values. Five (5) replicates of each sample were assayed. The mean observed/expected values were calculated. Average % recovery across 9 samples tested was 103%.

Linear regression of Observed versus Expected doses demonstrated excellent Goodness-of-Fit ($R^2 = 0.995$) with the following equation:

$$\text{Observed} = 0.97(\text{Expected}) + 0.062$$

1.15 Precision

Precision studies were performed in accordance with Clinical Laboratory Standard Institute (CLSI) guidance: *Evaluation of Precision Performance of Quantitative Methods; Approved Guideline-Second Edition.* CLSI document EP5-A2 (ISBN 1-56238-542-9). Two aliquots of each test sample were assayed in two runs per day on 20 different days. Analysis of variance was used to estimate the within-run and total variance.

Precision results for the IMMULITE 2000 Free T4 assay are as follows:

IMMULITE 2000 Free T4 Precision*

		Within-Run		Total	
Material / Sample #	Mean (ng/dL)	SD (ng/dL)	CV %	SD (ng/dL)	CV %
Pool 05	0.51	0.040	7.8	0.052	10.2
Pool 06	0.85	0.038	4.5	0.060	7.1
Control	1.13	0.067	5.9	0.072	6.4
Pool 07	1.49	0.072	4.8	0.090	6.0
Pool 08	2.91	0.103	3.5	0.104	3.6
Pool 09	4.82	0.144	3.0	0.172	3.6

* Data are representative of one lot on one instrument

1.16 Assay Specificity

1.16.1 Potential Interferents

The IMMULITE 2000 Free T4 assay was tested for interference by bilirubin, hemoglobin and triglycerides.

Presence of conjugated or unconjugated bilirubin in concentrations up to 20 mg/dL has no effect on the results of the assay.

Presence of hemoglobin in concentrations up to 634 mg/dL has no effect on the results of the assay.

Presence of triglycerides in concentrations up to 1000 mg/dL has no effect on the results of the assay.

1.16.2 Cross-reactivity

The IMMULITE 2000 Free T4 assay is highly specific for Free T4 with no detectable cross-reactivity to other naturally occurring compounds that might be present in patient samples, including L-T3, Diiodothyronine, Monoiodotyrosine, Diiodotyrosine, D-T4, Diphenylhydantoin (Phenytoin), Tetraiodothyroacetic Acid, Salicylic Acid, and Albumin.

1.17 Quality Control

The recommended control is the Siemens Medical Solutions Diagnostics' CON6 Multivalent Control Module. This control is a multi-constituent, human serum-based, tri-level control containing over 25 constituents commonly measured by immunoassay. It is intended strictly for *in vitro* diagnostic use as an aid in monitoring the day-to-day performance of assays for these constituents.

1.18 Sample Stability

Samples are stable for 2 days at 2–8°C, or 2 months frozen at –20°C[2]

1.19 *Assay Kit Stability*

1.19.1 Shelf Life

Kit stability testing was conducted on multiple lots of the IMMULITE 2000 Free T4 assay kit and included the following assessments:

- Real-time stability at long term package insert storage conditions
- Stress (accelerated) conditions to simulate storage/stress conditions that might occur during shipment to and storage at customer facilities. Stress studies also support real-time stability. Stress studies indicated below were conducted at initiation of the stability testing and repeated a minimum of 90 days later.
  - 3-Day storage at 37°C
  - 7-Day storage at room temperature (15-30°C)
  - 3 Freeze/thaw cycles (freeze -30°C to -5°C, thaw at 2-8°C)

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[2] Hay ID, Bayer MF, et al. American Thyroid Association assessment of current free thyroid hormone and thyrotropin measurements and guidelines for future clinical assays. Clin Chem 1991;37:2002-8.

The shelf life claim for the IMMULITE 2000 Free T4 assay kit is 330 days (unopened) when stored at 2-8°C.

1.19.2 On-board Reagent Stability

The Free T4 reagent is stable on-board the IMMULITE 2000 instrument after opening for 92 days.

1.19.3 Assay Adjustors and Controls Open Vial Stability

IMMULITE 2000 Free T4 Adjustors and Controls are stable at 2-8°C for 30 days or for 6 months (aliquoted) at -20 °C after reconstitution.

1.20 Method Comparison - Comparison of IMMULITE 2000 Free T4 to the Predicate Assay

Free T4 results of 282 samples were compared between IMMULITE 2000 Free T4 and the Predicate assay. Results indicate substantial equivalence.

IMMULITE 2000 (Y) vs. ADVIA Centaur FrT4 (X):

Linear Regression:

Y= 1.06X - 0.001;

Slope = 1.06 (95% CI 1.03 to 1.08);

Intercept = -0.001 (95% CI -0.04 to 0.04); r = 0.981

Mean IMMULITE 2000 Free T4:	1.43 ng/dL
Mean ADVIA Centaur FrT4	1.35 ng/dL
Sample range	0.3 – 5.2 ng/dL

1.21 *Conclusions*

The IMMULITE 2000 Free T4 assay demonstrates acceptable analytical performance including analytical sensitivity, precision, analytical specificity, and accuracy. Method comparison to the predicate demonstrated acceptable regression statistics and agreement of reference intervals. The IMMULITE 2000 Free T4 assay is therefore substantially equivalent to the FDA cleared predicate ADVIA Centaur FrT4 and thereby safe and effective for the following intended use:

> For *in vitro* diagnostic use with the IMMULITE 2000 Systems Analyzers — for the quantitative measurement of non-protein-bound thyroxine (free T4) in serum and heparinized plasma as an aid in the clinical assessment of thyroid status.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEB - 2 2009

Siemens Healthcare Diagnostics
c/o Philip Liu, Ph.D.
Manager, Regulatory Affairs and Compliance
511 Benedict Ave.
Tarrytown, NY 10591

Re: k083373
Trade Name: IMMULITE 2000 Free Thyroxine Assay
Regulation Number: 21 CFR 862.1695
Regulation Name: Free Thyroxine Test System
Regulatory Class: Class II
Product Codes: CEC
Dated: November 11, 2008
Received: November 14, 2008

Dear Dr. Liu:

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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. 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); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Courtney C. Harper, Ph.D.
Acting Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Indication for Use

510(k) Number (if known): k083373

Device Name: IMMULITE® 2000 Free Thyroxine Assay

Indication For Use:

The IMMULITE® 2000 Free Thyroxine Assay is for *in vitro* diagnostic use with the IMMULITE 2000 Systems Analyzers — for the quantitative measurement of non-protein-bound thyroxine (free T4) in serum and heparinized plasma, as an aid in the clinical assessment of thyroid status.

Prescription Use ___X___ And/Or Over the Counter Use ____.
(21 CFR Part 801 Subpart D) (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Carol C Benson

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) k083373