

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k160647

B. Purpose for Submission:

Adding pediatric reference intervals to previously cleared assays (cleared under k083373 and k970227)

C. Measurand:

Free thyroxine (FT4) and thyroid stimulating hormone (TSH)

D. Type of Test:

Quantitative, chemiluminescence immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

IMMULITE 2000 Third Generation TSH

IMMULITE 2000 Free T4

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:

For in vitro diagnostic use with the IMMULITE 2000 Systems Analyzers for the quantitative measurement of thyrotropin (TSH) in serum. Measurements of thyroid stimulating hormone produced by the anterior pituitary are used in the diagnosis of thyroid or pituitary disorders.

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. Measurements of free thyroxine are used in the diagnosis of thyroid disease.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

IMMULITE 2000 Systems

I. Device Description:

IMMULITE 2000 Free T4 set consists of the following reagents:

Free T4 Bead Pack – 200 beads coated with monoclonal murine anti-T4 antibody.

Free T4 Reagent Wedge – 11.5mL alkaline phosphatase (bovine calf intestine) conjugated to T4 in buffer.

Free T4 Adjustors – Two vials (low and high) of lyophilized free T4 in processed human serum, with preservative.

IMMULITE 2000 Third Generation TSH set consists of the following reagents:

TSH Bead Pack – 200 beads coated with monoclonal murine anti-TSH antibody.

TSH Reagent Wedge – 23 mL alkaline phosphatase (bovine calf intestine) conjugated to TSH in buffer (with preservative).

TSH Adjustors – Two vials (low and high) of lyophilized human TSH in a serum/buffer matrix.

TSH Sample Diluent – 25 mL of concentrated (ready-to-use) TSH-free serum/buffer matrix.

J. Substantial Equivalence Information:

1. Predicate device name(s):

IMMULITE 2000 Free T4
 IMMULITE 2000 Third Generation TSH

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

k083373, k970227

3. Comparison with predicate:

FT4 assay:

Similarities and Differences		
Item	Candidate device IMMULITE 2000 Free T4 (k160647)	Predicate device IMMULITE 2000 Free T4 (unmodified) (k083373)
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.	Same
Analyte	Free Thyroxine (T4)	Same
Instruments	IMMULITE 2000 Systems	Same
Analytical Measuring Range (Assay Range)	0.30 – 6.0 ng/dL (3.9 – 77.2 pmol/L)	Same
Infants (1-23 months) Reference Intervals	0.80 – 1.27 ng/dL (10.3 – 16.3 pmol/L)	None
Children (2-12 years) Reference Intervals	0.74 – 1.28 ng/dL (9.5 – 16.5 pmol/L)	None
Adolescents (13-20 years) Reference Intervals	0.75 – 1.27 ng/dL (9.7 – 16.3 pmol/L)	None
Euthyroid Adults (≥21 yrs) Reference Intervals	0.89 – 1.76 ng/dL (11.5 – 22.7 pmol/L)	Same

TSH assay:

Similarities and Differences		
Item	Candidate device IMMULITE 2000 Third Generation TSH (k160647)	Predicate device IMMULITE 2000 Third Generation TSH (unmodified) (k970227)
Intended Use	For in vitro diagnostic use with the IMMULITE® 2000 Systems Analyzers — for the quantitative measurement of thyrotropin (TSH) in serum.	Same
Analyte	Thyroid stimulating hormone (TSH)	Same
Instruments	IMMULITE 2000 Systems	Same
Analytical Measuring Range (Assay Range)	0.004 – 75 µIU/mL (mIU/L)	Same
Infants(1-23 months) Reference Intervals	0.83 – 6.5 µIU/mL (mIU/L)	None
Children(2-12 years) Reference Intervals	0.58 – 4.1 µIU/mL (mIU/L)	None
Adolescents (2-12 years) Reference Intervals	0.39 – 4.0 µIU/mL (mIU/L)	None
Euthyroid Adults (≥21 yrs) Reference Intervals	0.4073 – 4.0 µIU/mL (mIU/L)	Same

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

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

L. Test Principle:

IMMULITE 2000 Free T4: 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 first incubated together with the coated bead. During this time, free T4 in the sample competes with enzyme conjugated T4 in the reagent for a limited number of antibody binding sites on the bead. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the

signal is generated in proportion to the bound enzyme.

IMMULITE 2000 Third Generation TSH: IMMULITE 2000 Third Generation TSH is a solid-phase, two-site chemiluminescent immunometric assay. The solid phase (bead) is coated with monoclonal murine anti-TSH antibody. The liquid phase consists of alkaline phosphatase (bovine calf intestine) conjugated to polyclonal goat anti-TSH antibody. The patient sample and the reagent are incubated together with the coated bead for 60 minutes. During this time, TSH in the sample binds to enzyme conjugated anti-TSH antibody in the reagent, and then this complex is captured by the anti-TSH antibody on the bead. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Provided in k083373 and k970227.

b. Linearity/assay reportable range:

Provided in k083373 and k970227.

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

Provided in k083373 and k970227.

d. Detection limit:

Provided in k083373 and k970227.

e. Analytical specificity:

Provided in k083373 and k970227.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

Provided in k083373 and k970227.

b. *Matrix comparison:*

Provided in k083373 and k970227.

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:

IMMULITE 2000 Free T4: A pediatric reference range study using population age from 1 month old to 20 years old was conducted. Serum samples were collected at 8 U.S. sites to be representative of the U.S. population diversity. The samples were obtained from apparently healthy individuals who were not taking prescribed or over-the-counter medications in the 7 days prior to sample collection, or were not taking contraceptive medication in the 90 days prior to sample collection, or were not pregnant. Subject who are suspicious of premature/delayed puberty, or are positive for the presence of autoantibody against Thyroid Peroxidase (TPO) and Thyroglobulin (TG) are also excluded from the study. All samples were shipped and tested at a single laboratory study site. A total of 426 pediatric patient (81 infants, 197 children, and 148 adolescents) samples were tested in singleton using four (4) reagent lots to establish the IMMULITE 2000 Free T4 reference ranges for the studied pediatric population. Results from the 2.5th to 97.5th percentile were used as the pediatric reference ranges. The reference interval for the infant group was calculated using the robust symmetrical 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 based on the CLSI C28-A3 recommendation because the sample size was greater than 120. Reference ranges are summarized in the table below.

Age Range	Reference Ranges
Infants (01 – 23 months)	0.80 – 1.27 ng/dL
Children (02 – 12 years)	0.74 – 1.28 ng/dL
Adolescents (13 – 20 years)	0.80 – 1.27 ng/dL

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

	Lower Limit of reference range	Upper Limit of reference
90% confidence intervals:	0.76 – 0.84 ng/dL	1.23 – 1.32 ng/dL

IMMULITE 2000 Third Generation TSH: A pediatric reference range study using population age from 1 month old to 20 years old was conducted. Serum samples were collected at 8 U.S. sites to be representative of the U.S. population diversity. All samples were shipped and tested at a single laboratory study site. A total of 433 pediatric patient (90 infants, 195 children, and 148 adolescents) samples were tested in singleton using three (3) reagent lots to establish the IMMULITE 2000 Third Generation TSH reference ranges for the studied pediatric population. Results from the 2.5th to 97.5th 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 language in 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 based on the CLSI C28-A3 recommendation because the sample size was greater than 120. Reference ranges are summarized in the table below.

Age Range	Reference Ranges
Infants (01 – 23 months)	0.83 - 6.5 μ IU/mL
Children (02 – 12 years)	0.58 - 4.1 μ IU/mL
Adolescents (13 – 20 years)	0.39 - 4.0 μ IU/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:	0.70 – 0.99 μ IU/mL	5.58 – 7.65 μ IU/mL

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.