DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

March 3, 2016

Siemens Healthcare Diagnostics, Inc.
Susan Brocchi
Regulatory Clinical Affairs Specialist
511 Benedict Avenue
Tarrytown NY 10591

Re: K152061
Trade/Device Name: Immulite 200 TSI Assay, Immulite 200 TSI Calibration Verification Material
Regulation Number: 21 CFR 866.5870
Regulation Name: Thyroid autoantibody immunological test system
Regulatory Class: II
Product Code: JZO
Dated: February 3, 2016
Received: February 4, 2016

Dear Ms. Brocchi:

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,

Kelly Oliner -S

For,
Leonthena R. Carrington, MS, MBA, MT(ASCP)
Director
Division of Immunology and Hematology 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)*
K152061

Device Name
IMMULITE®2000 TSI Assay
IMMULITE®2000 TSI Calibration Verification Material (CVM)

Indications for Use *(Describe)*
The IMMULITE® 2000 TSI (thyroid-stimulating immunoglobulins) Assay is an in vitro diagnostic immunoassay for the semi-quantitative determination of thyroid stimulating autoantibodies specific to thyroid stimulating hormone receptors (TSHR) in human serum (including Serum Separator tubes) or plasma (K2-EDTA or lithium heparin). The IMMULITE® 2000 TSI Assay is for use on the IMMULITE® 2000 system. The measurement of thyroid stimulating autoantibodies, in conjunction with other clinical and laboratory findings, is used as an aid in the diagnosis of patients suspected of having Graves' disease.
The IMMULITE® TSI Calibration Verification Material (CVM) is for in vitro diagnostic use in the verification of calibration of the IMMULITE® TSI Assay on the IMMULITE® 2000 Systems.

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.

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IMMULITE® 2000 TSI Assay
510(k) Summary as Required by 21 CFR 807.92

A. 510(k) Number:
K152061

B. Purpose for Submission:
New Device

C. Measurand:
Thyroid-stimulating immunoglobulins

D. **Type of test:**
Semi-quantitative chemiluminescent immunometric assay

E. **Applicant:**
Siemens Laboratory Diagnostics Inc.

F. Proprietary and Established Names:
IMMULITE®2000 TSI Assay
IMMULITE®2000 TSI Calibration Verification Material

G. Regulatory Information:

Regulation Section	Classification	Product Code	Panel
21 CFR 866.5870, Thyroid autoantibody immunological test system	Class 2 (Performance Standards)	JZO – System, Test, Thyroid Autoantibody	Immunology (82)
21 CFR 862.1150	Class 2	JIT, Calibrator, secondary	Clinical Chemistry (75)
21 CFR 862.1660, Quality control material (assayed and unassayed)	Class 1, reserved	JJX, Single analyte control	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   The IMMULITE® 2000 TSI (thyroid-stimulating immunoglobulins) Assay is an in vitro diagnostic immunoassay for the semi-quantitative determination of thyroid stimulating autoantibodies specific to thyroid stimulating hormone receptors (TSHR) in human serum (including Serum Separator tubes) or plasma (K2-EDTA or lithium heparin). The IMMULITE® 2000 TSI Assay is for use on the IMMULITE® 2000 system. The measurement of thyroid stimulating autoantibodies, in conjunction with other clinical and laboratory findings, is used as an aid in the diagnosis of patients suspected of having Graves' disease.

   The IMMULITE® TSI Calibration Verification Material (CVM) is for in vitro diagnostic

use in the verification of calibration of the IMMULITE® TSI Assay on the IMMULITE® 2000 Systems.

2. Indication(s) for use:
   See Intended Use above
3. Special conditions for use statement(s):
   For prescription use only
4. Special instrument requirements:
   Only for use on the IMMULITE 2000 Analyzer (k970227)

I. Device Description:

The IMMULITE 2000 TSI assay kit consists of the following components:

- TSI bead pack coated with MAb (3D7) anti-TSHR anchor antibody and hTSHR Capture Chimera
- TSI reagent wedge containing hTSHR-Chimera alkaline phosphatase conjugate
- TSI adjustors: low and high, containing TSI negative heat-inactivated bovine serum and thyroid stimulating human MAb (M22)
- TSI controls: negative, low, and high, containing TSI negative human serum and thyroid stimulating MAb (M22)
- Multi-Diluent 2

J. Substantial Equivalence Information:

1. Predicate device names(s) and 510(k) number(s):
   Thyretain TSI Reporter BioAssay, k092229
   Elecsys Anti-TSHR Immunoassay, k080092
   Elecsys Anti-TSHR CalCheck, k080643

2. Comparison with predicate:

ASSAY SIMILARITIES – Predicate 1		
Item	**Device**	**Predicate 1**
	IMMULITE 2000 TSI Assay	**Thyretain TSI Reporter BioAssay**
Analyte	TSH receptor stimulating autoantibodies	same
Signal	Chemiluminescence	same
Detection method	Luminometry	same
Controls	3 (negative, low, and high)	3 (negative, reference, positive)

ASSAY DIFFERENCES – Predicate 1		
Item	**Device**	**Predicate**
	IMMULITE® 2000 TSI Assay	**Thyretain TSI Reporter BioAssay**

Intended Use	The IMMULITE® 2000 TSI (thyroid-stimulating immunoglobulins) Assay is an in vitro diagnostic immunoassay for the semi-quantitative determination of thyroid stimulating autoantibodies specific to thyroid stimulating hormone receptors (TSHR) in human serum (including Serum Separator tubes) or plasma (K2-EDTA or lithium heparin). The IMMULITE® 2000 TSI Assay is for use on the IMMULITE® 2000 system. The measurement of thyroid stimulating autoantibodies, in conjunction with other clinical and laboratory findings, is used as an aid in the diagnosis of patients suspected of having Graves' disease.	Intended for the qualitative detection in serum of thyroid stimulating autoantibodies to the thyroid stimulating hormone receptors (TSHRs) on the thyroid. The detection of these stimulating autoantibodies, in conjunction with other clinical and laboratory findings, may be useful as an aid in the differential diagnosis of patients with Graves' disease.
Assay Principal	Immunometric	Cell-based Bioassay
Sample matrix	Serum or plasma	Serum
Assay format	Semi-quantitative	Qualitative
Unit of measure	IU/L	SRR% (sample to reference ratio)
Solid phase	Polystyrene bead coated with hTSHR capture chimera	CHO Mc4 cell monolayer
Traceability	NIBSC Standard 08/204	NISBC Standard 03/192
Sample size	50 uL	40 uL
Measuring range	0.10-40 IU/L	N/A (qualitative)
Incubation time	60 minutes	3 hours
LoB	0.03 IU/L	62.75%
LoD	0.06 IU/L	89.14%
Assay Cut-off	0.55 IU/L	140%

ASSAY SIMILARITIES – Predicate 2		
Item	**Device**	**Predicate 2**
	IMMULITE 2000 TSI Assay	**Elecsys Anti-TSHR Immunoassay**
Analyte	TSH receptor stimulating autoantibodies	Same

Unit of measure	IU/L	Same
Sample size	50µL	Same

ASSAY DIFFERENCES – Predicate 2		
Item	**Device**	**Predicate**
	IMMULITE® 2000 **TSI Assay**	**Elecsys Anti-TSHR Immunoassay**
Intended Use	The IMMULITE® 2000 TSI (thyroid-stimulating immunoglobulins) Assay is an in vitro diagnostic immunoassay for the semi-quantitative determination of thyroid stimulating autoantibodies specific to thyroid stimulating hormone receptors (TSHR) in human serum (including Serum Separator tubes) or plasma (K2-EDTA or lithium heparin). The IMMULITE® 2000 TSI Assay is for use on the IMMULITE® 2000 system. The measurement of thyroid stimulating autoantibodies, in conjunction with other clinical and laboratory findings, is used as an aid in the diagnosis of patients suspected of having Graves' disease.	An immunoassay for the in vitro quantitative determination of autoantibodies to TSH receptor in human serum using a human thyroid stimulating monoclonal antibody. The anti-TSH receptor determination is used in the assessment of patients with suspect Graves' disease (autoimmune hyperthyroidism). The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.
Sample matrix	Serum or plasma	Serum
Controls	3 (negative, low, and high)	2 (positive and negative)
Detecting Antibody	hTSHR AP detection Chimera	M22
Assay Protocol	Bridge Format	Competition Principle
Detection Protocol	Chemiluminescence	Electrochemiluminescence
Traceability	NIBSC Standard 08/204	NISBC Standard 90/672
Incubation	60 Minutes	27 Minutes
LoB	0.03 IU/L	0.500 IU/L
LoD	0.06 IU/L	0.800 IU/L
LoQ	0.10 IU/L	0.900 IU/L
Reportable Range	0.10-40 IU/L	0.800 – 40.0 IU/L
Assay Cut-off	0.55 IU/L	1.75 IU/L

Calibrator Verification Materials SIMILARITIES		
Item	**Device**	**Predicate**
	IMMULITE® 2000 TSI CVM	**Elecsys Anti-TSHR CalCheck**
Form	Lyophilized	Same
Stability	Stable unopened until the expiration date.	Same
Use	Single Use Only	Same
Analyte	Thyroid Stimulating IgG	Same
Storage	2-8°C	Same
Calibrator Verification Materials DIFFERENCES		
Item	**Device**	**Predicate**
	IMMULITE® 2000 TSI CVM	**Elecsys Anti-TSHR CalCheck**
Intended Use	The IMMULITE® TSI Calibration Verification Material (CVM) is for in vitro diagnostic use in the verification of calibration of the IMMULITE® TSI Assay on the IMMULITE® 2000 Systems.	For use in the verification of calibration established by the Elecsys Anti-TSHR reagent on the indicated Elecsys and cobas e immunoassay analyzers.
Instrumentation	Siemens IMMULITE® 2000	Roche Elecsys and cobas e
Sample Matrix	Bovine serum with preservatives	Human serum
Number of levels	4	3

K. Standard/Guidance Documents Referenced:

CLSI EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods, Approved Guideline – Second Edition

CLSI EP06-A, Evaluation of Linearity of Quantitative Measurement Methods: A Statistical Approach – First Edition

CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

CLSI EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples – Third Edition

CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

CLSI EP24-A2, Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline – Second Edition

CLSI EP25-A, Evaluation of Stability of in vitro Diagnostic Reagents; Approved Guidance – First Edition

CLSI EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory – Third Edition

L. Test Principle:

The IMMULITE 2000 TSI assay is an automated, two-cycle, chemiluminescent immunoassay. It employs two recombinant chimeric human TSH receptors (hTSHR) where the major epitope for the blocking antibody is replaced. The capture receptor is immobilized on the solid phase (polystyrene bead) by 3D7, a monoclonal antibody directed against the C-terminus of hTSHR. In the first 30-minute cycle, thyroid stimulating antibodies in the patient sample bind through one arm to the capture receptor on the polystyrene bead. Upon completion of the 1st cycle, the bead is washed 4X with water onboard the instrument. In the second cycle, a liquid reagent containing the signal receptor is added to the reaction tube and incubated for 30-minutes. The immobilized TSI binds the signal receptor through the second arm forming a bridge. Unbound signal receptor is then removed by four centrifugal water washes. Finally, chemiluminescent substrate is added to the reaction tube and a signal is generated in direct relation to the amount of bound signal receptor and TSI in the sample.

M. Performance Characteristics

1. Analytical Performance:
   a. *Precision/Reproducibility:*
   Precision was evaluated using a protocol based on CLSI document EP05-A2. Six serum samples and the low and high kit controls were tested. Serum samples were prepared by mixing positive samples into negative sample pools in order to reach the desired concentration.

   Each sample was tested in duplicate in two runs per day over 20 days, for a total of 80 replicates. One instrument was used, and one lot of the device was tested for a total of 80 replicates per sample. Precision was calculated using Nested Analysis of Variance.

20-Day Imprecision N=80		Repeatability		Within Lab	
Sample	**Mean IU/L**	**SD**	**%CV**	**SD**	**%CV**
L2SIC1	1.04	0.05	4.9	0.06	5.4
L2SIC2	21.27	0.96	4.5	1.21	5.7
SERP1	0.34	0.02	7.0	0.03	8.3
SERP2	0.69	0.03	4.1	0.03	5.0
SERP3	1.57	0.07	4.4	0.08	5.3
SERP4	4.43	0.18	4.0	0.26	5.9
SERP5	7.80	0.27	3.5	0.42	5.4
SERP6	29.09	1.91	6.6	2.11	7.3

b. *Linearity/assay Reportable Range:*

IMMULITE 2000 TSI Linearity was evaluated according to CLSI EP6-A. TSI positive and TSI negative samples were obtained from several commercial vendors. Sample sets were prepared gravimetrically pooling low and high samples.

Conclusion

Linearity data for % Difference was shown to be ± 15% or 0.50 IU/L (whichever is greater) for most samples; tested within range 0.50 – 40.0 IU/L with calibrators and pooled samples. Because of the heterogeneity of TSHR autoantibodies, certain patient samples may exhibit a non-linear dilution.

c. *Traceability, Stability, Expected Values (controls, calibrators, methods):*

Traceability:

The IMMULITE® 2000 TSI assay is traceable to NIBSC standard 08/204 and is manufactured using qualified materials and measurement procedures.

The instrument-stored assay calibration curve is based on a series of calibrators covering the claimed assay range and is specific for each lot of the assay.

Assay and component stability:

Real time shelf life stability testing to support the following claims for the unopened devices and opened components:

Acceptance criteria for all components of the assay was assessed based on analyte drift as described in CLSI document EP25-A. The dose value of the component should be within the limits described in the table below except if below the LoQ of 0.10 IU/L where recovery cannot be properly determined. At each time point, all Control results must be within Quality Control established range, to validate the run.

Component on Stability	Parameter	Drift Specifications
Reagents and Beads	Control 1 at ≤ -60°C	≤ 15% from Day 0 mean
Reagents and Beads	Control 2 at ≤ -60°C	≤ 10% from Day 0 mean
Reagents and Beads	CVM 1 at ≤ -60°C	≤ 0.15 IU/L from Day 0 mean
Reagents and Beads	MDP 1	≤ 20% from Day 0 mean
Reagents and Beads	MDP 4	≤ 10% from Day 0 mean
Reagents and Beads	Cal J	≤ 10% from Day 0 mean

Closed vial testing (kit stored at 2 – 8 °C) was conducted at 0, 60, 120, 180, 270, 360, 450, and 540 days. Four replicates for the Low and High Adjustors and four replicates of each Control, MDP, and Calibrator J were run on each day of the study. Dose values of the Controls and samples were calculated from the Day 0 adjustment and from the adjustment performed on each subsequent day of testing.

Open vial/kit testing of components stored at 2 – 8°C was conducted at Days 0, 7, 8, 14, 30, 45, 60, 90, and 97. Open vial testing of aliquotted components stored at -20°C was conducted on Days 0, 30, 60, 90, 120, 150, 180, and 194. Four replicates of each Adjustor and four replicates of each Control were run on each day of the study.

Component	Storage	Stability Claim
Kit, unopened	2 – 8 °C	12 Months
Bead Pack, open	2 – 8 °C	90 Days
Reagent wedge, open and on-board	2 – 8 °C	90 Days
Sample diluent, open (L2M2Z, L2M2Z4)	2 – 8 °C	30 Days
Sample diluent, open frozen aliquoted (L2M2Z, L2M2Z4)	-20 °C	6 Months
Adjustors open (L2SIL, L2SIH)	2 – 8 °C	90 Days
Adjustors (L2SIL, L2SIH) frozen aliquotted	-20 °C	4 Months
Controls open (L2SIC1, L2SIC2)	2 – 8 °C	90 Days
Controls (L2SIC1, L2SIC2) frozen aliquotted	-20 °C	6 Months
CVM, unopened	2 – 8 °C	12 Months
CVM, opened and reconstituted	2 – 8 °C	30 Days

Sample stability:

The sample stability study supports the claim of stability for 24 hours at 20 - 25°C, 7 days at 2 – 8ºC, and 12 months at -20°C for serum and plasma.

Adjustment interval (calibration curve) stability:

Real time testing supported the recommended adjustment interval of four weeks.

d. *Detection Limit:*

Limit of Blank (LoB): Five TSI negative samples were analyzed on three IMMULITE® 2000 instruments over 3 days. The samples were tested using three lots of reagent for 2 runs with 2 replicates per run. The LoB result was determined by applying a nonparametric principle based on ranked ordered value using the following equation where p= (100-α) = 95 and NB = number of blank measurements = 180:

$$\text{LoB rank position} = [N_B(p/100)+0.5]$$

The LoB was the 171.5^{th} ranked result. The LoB was analyzed for each of the 3 lots. The highest LoB by lot was determined to be 0.03 IU/L.

Limit of Detection (LoD): Five TSI serum samples (mean concentrations ranging from 0.016 to 0.110 IU/L) were assayed in replicates of 4 using 3 reagent kit lots run for 3 days on 3 systems. Thirty-six observations were obtained for each sample. The LoD was determined by the following equation:

$$\text{LoD} = \text{LoB} + c_p SD_L$$

The LoD was analyzed for each of the 3 lots. The highest LoD by lot was determined to be 0.06 IU/L.

e. *Analytical Specificity:*

Endogenous interferents:

Three serum pools with concentrations across the assay range were prepared and spiked separately with endogenous interferents. A control sample was prepared for each interfering substance by spiking the appropriate diluent at the same volume as the interfering substance; each sample was tested in triplicate. The interferents tested were: Intralipid (500 and 1000 mg/dL); Hemoglobin (200 and 500 mg/dL); Bilirubin: Conjugated and Unconjugated (20 and 40 mg/dL each); and K_2-EDTA (9mg/mL). Heterophile samples, HAMA and Rheumatoid Factor, were also evaluated.

No interference (≤ 10% different than control sample) was found when the means of control samples were compared to the means of the spiked samples, except in the case of hemoglobin. The sponsor has included limitations to this effect in the package insert: "Presence of hemoglobin at a concentration of 200mg/dL or higher may affect recovery."

Samples spiked with a five-fold excess of K_2-EDTA anticoagulant were compared to normal serum to investigate the effect of a short blood draw on TSI assay results. Three samples were tested; all but one showed recovery within ± 10% of the serum control value. The sponsor has included limitations to this effect in the package insert: "Short Draw K_2-EDTA Plasma samples may result in under-recovery of IMMULITE 2000 TSI results."

HAMA Study:

TSI samples were prepared at three target concentrations across the assay range. Samples were divided into control groups (spiked with HAMA negative serum) and test groups (spiked with HAMA positive serum to final HAMA concentration of 10 ng/mL or 40 ng/mL). Mean values for each sample were determined on IMMULITE 2000 (n=12) and the percent (%) difference from the control samples was calculated.

The assay demonstrated individual sample bias of <4% when evaluated at the 10 ng/mL and 40 ng/mL of HAMA.

Rheumatoid Factor (RF) Study:

TSI samples were prepared at three target concentrations across the assay range. Samples were divided into control groups (spiked with RF negative serum) and test groups (spiked with RF positive serum to final RF concentration of 100 IU/mL or 200 IU/mL). Mean values for each sample were determined on IMMULITE 2000 (n=12) and the percent (%) difference from the control samples was calculated.

The assay demonstrated individual sample bias of <5% when evaluated at the 100 IU/mL and 200 IU/mL of RF.

Cross Reactivity:

Six (6) potential biological interferent samples (TSH, FSH, LH, hCG, aTPO, and aTG) were prepared by spiking known concentrations into three TSI serum pools spanning the analytical measuring range of the assay.

The assay demonstrated cross-reactivity bias of ≤10% for all interferents and all samples.

f. *Assay cut-off:*

The cut-off of the IMMULITE® 2000 TSI assay was determined with positive and negative patient samples by a ROC analysis, with a balanced consideration of sensitivity and specificity. A total of 434 samples were used, consisting of 164 Graves' disease patient samples and 270 samples with other thyroid or autoimmune diseases**.** A result ≥ 0.55 IU/L indicates hyperthyroid Graves' disease. A result of < 0.55 IU/L indicates the patient does not have Graves' disease or is in remission.

2. Comparison Studies
   a. *Method Comparison with predicate device:*

The Thyretain TSI Reporter BioAssay, a qualitative assay for the detection of stimulating thyroid hormone receptor (TSHR) autoantibodies, was identified as the predicate device.

A method comparison was performed to compare the performance of the IMMULITE 2000 TSI assay to the Thyretain™ TSI Reporter BioAssay using 811 serum samples from patients with Graves' disease, other thyroid or autoantibody diseases. Specimens were tested using the IMMULITE 2000 TSI assay at two external sites and one internal site. Specimens were tested using the Thyretain device at one of the external sites

IMMULITE 2000 TSI	THYRETAIN TSI Reporter BioAssay	
	Negative	Positive
Negative	422	14
Positive	59	316
Total	481	330

Positive Agreement: 95.8% (95% CI: 93.0 – 97.7)

Negative Agreement: 87.7% (95% CI: 84.5 – 90.5)

Overall Agreement: 91.0% (95% CI: 88.8 – 92.9)

   b. *Matrix Comparison:*

Graves' Disease sets of matched serum and plasma samples were collected in the following anti-coagulant tubes: serum clot tube, lithium heparin plasma tube, serum separator tube (SST), and K_2-EDTA plasma tube. Sample concentrations spanned the analytical measuring range of the assay. Data was analyzed using Passing & Bablock regression plots. Results were as follows:

Serum vs.	Slope	Intercept	Correlation Coefficient
SST Serum	1.01	0.00	0.99
K_2-EDTA Plasma	1.03	-0.01	0.99
Lithium	0.99	-0.01	0.99

Heparin Plasma			

3. Clinical Studies:
   a. *Clinical Sensitivity and Specificity*

Clinical Sensitivity and Specificity: Serum samples from 361 treated and untreated hyperthyroid Graves' disease patients, and 404 individuals with other thyroid or autoimmune diseases were evaluated. The TSI values for the negative patients with other thyroid or autoimmune diseases had an upper limit of 0.39 IU/L. At the 0.55 IU/L cut-off, the clinical sensitivity and specificity were 98.6% and 98.5% respectively (see Clinical Sensitivity and Specificity table).

In this clinical study, 3.6% (4/111) of the Hashimoto's thyroiditis (HT) patients were TSI positive. Two of the four HT patient samples were also positive in other commercially available TSI or Anti-TSHR assays. The third HT patient was biochemically hyperthyroid at the time of HT diagnosis. The simultaneous occurrence of HT and Graves' disease, although rare, has been reported in the literature. The fourth HT patient had a TSI result of 0.69 IU/L, slightly above the assay cut-off. Other clinical studies have detected TSI in 7% of HT patients without thyroid–associated orbitopathy (TAO) and in over 68% of the HT patients with TAO.

Sample Distribution of Other Diseases

Other Thyroid and Autoimmune Disease Samples	**n**
Multinodular goiter	26
Hashimoto's thyroiditis	111
Thyroid Cancer	37
Systemic Lupus Erythematosus	25
Rheumatoid Arthritis	25
Ulcerative Colitis	25
Diabetes (Type 1 & 2)	20
Celiac Disease	30
Crohn's Disease	25
Toxic multinodular goiter	6
Sub-acute thyroditis	6

Addison's Disease	13
Sjögren's Syndrome	22
Other diseases	33
TOTAL	404

Clinical Sensitivity and Specificity

IMMULITE 2000 TSI	**Graves' Disease Diagnosis**	
	Negative	Positive
Negative	398	5
Positive	6	356
Total	404	361

Clinical Sensitivity: 98.6% (95% CI: 96.8 – 99.5)
Clinical Specificity: 98.5% (95% CI: 96.8 – 99.5)

b. Other clinical supportive data:
Not applicable.

4. Clinical cut-off:
Not applicable.

5. Expected values/Reference range:

A total of 842 serum samples from apparently healthy males (n = 151), non-pregnant females (n = 155), first trimester (n = 169), second trimester (n = 191), and third trimester (n = 176) pregnant donors were analyzed using the IMMULITE 2000 TSI assay. The results from this study suggest a nonparametric 97.5th percentile of < 0.10 IU/L.

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.