510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE

A. 510(k) Number:
k041014

B. Purpose for Submission:
Clearance of new device

C. Analyte:
Thyrotropin (TSH)

D. Type of Test:
Quantitative Immunoradiometric assay

E. Applicant:
DiaSorin, Inc.

F. Proprietary and Established Names:
TSH-CTK-3 IRMA

G. Regulatory Information:
1. Regulation section:
   21 CFR § 862.1690, Thyroid stimulating hormone test system
   862.1150, Calibrator
   862.1660, Quality control material (assayed and unassayed)
2. Classification:
   Class II
3. Product Code:
   JLW, Radioimmunoassay, thyroid-stimulating hormone
   JIT, Calibrator, secondary
   JJX, Single (specified) analyte controls (assayed and unassayed)
4. Panel:
   Clinical Chemistry (75)

H. Intended Use:
1. Intended use(s):

The DiaSorin TSH-CTK-3 IRMA is an immunoradiometric assay for the quantitative determination of thyrotropin (TSH) in human serum.

Measurements of TSH levels are used as an aid in the diagnosis of thyroid or pituitary disorders.

2. Indication(s) for use:

See Intended Use section above

3. Special condition for use statement(s):
For professional use only in clinical laboratory settings

4. Special instrument Requirements:
General high complexity laboratory equipment, gamma counter

I. Device Description:

The TSH-CTK-3 IRMA kit consists of a radiolabeled tracer containing mouse monoclonal anti-intact TSH antibodies in buffer, tubes coated with mouse monoclonal anti-TSH-β antibodies, wash buffer, calibrators and control materials.

J. Substantial Equivalence Information:
1. Predicate device name(s):
    Ventrex hTSH ^{125}I IRMA
2. Predicate K number(s):
    k920856
3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended use	For in vitro diagnostic use. For the quantitative determination of thyrotropin (TSH) in human serum. Measurements of TSH are used as an aid in the diagnosis of thyroid or pituitary disorders.	For in vitro diagnostic use. For the quantitative determination of thyrotropin (TSH) in human serum.
Assay type	IRMA	IRMA
Coated tube	Mouse monoclonal anti-hTSH antibodies	Mouse monoclonal anti-hTSH antibodies
Tracer	^{125}I labeled mouse monoclonal anti-hTSH antibodies	^{125}I labeled goat anti-hTSH
Standards	7 levels – human serum based	8 levels – porcine serum based
Differences		
Item	**Device**	**Predicate**
Kit Controls	3 levels – human serum based	None

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

NCCLS Guideline EP6-A – Evaluation of the Linearity of Quantitative Analytical
Methods
NCCLS Guideline EP5-A – Evaluation of Precision Performance of Clinical Chemistry
Devices
NCCLS Guideline EP7-A – Interference Testing in Clinical Chemistry

L. Test Principle:
Sample and tracer antibody solution are added to the antibody coated tubes. TSH in the
sample reacts with both the antibody on the tube and the radiolabeled tracer antibody to
form a sandwich complex on the inner surface of the tube. Wash steps remove excess
material and radioactivity in the tube is measured in a gamma counter. The amount of
radioactivity in the tube is proportional to the amount of TSH in the sample. The
concentration is extrapolated from a standard curve generated from the kit calibrators and
verified by the kit controls.

M. Performance Characteristics (if/when applicable):
1. Analytical performance:
   a. *Precision/Reproducibility:*

Four serum pools were assayed in duplicate twice a day for 20 days (total n = 80
replicates). Multiple technicians and multiple kit lots were used in the analysis. In
addition, 2 serum pools with TSH values below 0.6 mU/L were assayed in quadruplicate
once per day for five days. Results for intra- and Inter-assay precision are summarized
below (units = mU/L).

Pool	Mean	Intra-Assay		Inter-Assay	
		SD	% CV	SD	% CV
1	0.136	0.014	10.6	0.018	13
2	0.187	0.008	4.6	0.024	13
A	0.6	0.04	6	0.1	12
B	1.6	0.1	5	0.1	7
C	16.8	0.3	2	0.8	5
D	40.8	0.8	2	2	5

   b. *Linearity/assay reportable range:*

The reportable range of this assay is determined by the range of the calibrators
determining the standard curve and the functional sensitivity of the assay. This device
contains calibrators from 0.02 to 80 mU/L TSH. The useable range is 0.09 to 80 mU/L.

Eight serum pools spanning the reportable range were tested in quadruplicate. Results
are summarized below (units = mU/L).

Sample	Expected Value	Mean Observed Value
1	0.125	0.09
2	10.11	8.87
3	20.1	19.3
4	30.09	29.14
5	40.08	39.62
6	50.06	47.9
7	60.05	56.3
8	70.04	63.85

Observed = 0.93(Expected) + 0.52; r = 0.998

Seven samples were diluted with zero standard to span the reportable range and were tested in duplicate. Results are summarized below (units = mU/L).

Observed = 1.02(Expected) + 0.19; r = 0.999

Recovery was evaluated by the addition of known amounts of TSH to 11 serum samples. Percent recoveries ranged from 97 -101% of expected..

c. Traceability (controls, calibrators, or method):

The kit contains a 7 point calibrator set to be run in duplicate with every assay. A standard curve generated from the results provides the basis for extrapolation of sample TSH concentration. The calibrators are made by adding human TSH gravimetrically to human serum matrix that has been previously stripped of endogenous TSH. The calibrators are traceable to a Master calibration curve that is standardized to the WHO 2nd IRP 80/558. The targeted TSH values for the 7 calibrators are 0.02, 0.16, 0.31, 1.25, 5.0, 20, and 80 mU/L TSH. Actual concentrations are provided with each kit.

The kit contains 3 levels of controls which are prepared gravimetrically by the addition of human TSH into a human serum based matrix that has been previously stripped of endogenous TSH. The controls are validated against 3 lots of calibrators and the actual values are provided with each kit.

d. Detection limit:

Functional sensitivity was determined by measuring 14 samples assayed in quadruplicate once a day for 5 days. The concentration at which assay imprecision was calculated to be 20 % CV (by interpolation) is 0.09 mU/L.

The analytical sensitivity, defined as the lowest concentration of TSH that can be distinguished from the zero standard by 2 standard deviations, was assessed by measuring 40 replicates of the zero standard. A corresponding standard curve was generated using the mean of the 40 measurements as the zero standard, and the concentration at 2 SD above the zero was determined to be 0.04 mU/L.

The potential for a high dose hook effect was evaluated for this assay by serially diluting a stock solution containing 200,000 mU/L TSH with zero calibrator down to 0.4 mU/L. Effects were observed above the range of the highest calibrator. The package insert will reflect the data (summarized below) and state that results above the highest calibrator should be reported as "> highest calibrator" or may need to be diluted further until a result is achieved in the range of the assay. (units = mU/L)

Expected	Observed
200000	0.72
100000	2.2
50000	2.91
25000	6.18
12500	12.7
6250	42.6
3125	125
1563	149
781	149
391	146
195	119
98	8.4
49	40
24	18.9
12	8.9
6	4.33
3	2.16
1.5	1.14
0.8	0.57
0.4	0.26

e. *Analytical specificity:*

To test the crossreactivity of this device to similar endogenous analytes, serum samples were spiked with the analyte and compared to a non-spiked base pool. No analytes tested significantly cross-reacted in this analysis. Results are summarized below:

Analyte	Concentration of Spiked Analyte	% Cross Reactivity
FSH	1400 mIU/mL	0.0001
LH	5500 mIU/mL	0.00003
hCG	71210 mIU/mL	0.000001

Three levels of control serum were tested in the presence of increasing levels of hemoglobin, bilirubin, cholesterol, or triglycerides to determine any interferences. No

interference was seen up to 500 mg/dL hemoglobin and up to 1000 mg/dL cholesterol. Bilirubin interferes with the assay results at and above 30 mg/dL. Triglycerides interfere with the assay results at and above 330 mg/dL.

The effect of Human Anti-Mouse Antibodies (HAMA) was evaluated. Eleven HAMA samples were tested neat and spiked with a TSH pool. Percent Recovery was then evaluated. No interference was observed in the presence of HAMA antibodies. However, the sponsor has included a cautionary statement in their labeling stating that HAMA samples may cause falsely low or elevated results.

     f. Assay cut-off:
        Not Applicable
  2. Comparison studies:
     a. Method comparison with predicate device:

Serum samples (n = 95 samples, including 39 purchased samples and 25 samples spiked to achieve samples with high TSH values) were tested in duplicate using the device and the predicate and compared. The results are summarized as follows:

Device = 1.08(Predicate) + 0.22; r = 0.99

     b. Matrix comparison:

Serum samples from 46 apparently healthy donors were aliquoted and matched samples were stored at 4°C or -20°C, respectively. The samples were then tested and compared to establish whether frozen samples were equivalent to fresh samples in this assay. No significant differences were observed between the two sets of matched samples.

  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:

Serum samples from 100 apparently healthy adults were assayed with the device. Donors had no known thyroid illness nor were they taking medications known to affect thyroid function. Results of the reference range study for this device in serum are summarized below.

Number of Subjects	100
Mean	1.35 mU/L

Median   1.13 mU/L
1 SD   0.85
Range   0.25 – 3.51 mU/L

N. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.