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

A. 510(k) Number:

k150879

B. Purpose for Submission:

New Device

C. Measurand:

Parathyroid Hormone

D. Type of Test:

Quantitative, Chemiluminescent Immunoassay

E. Applicant:

DiaSorin Inc.

F. Proprietary and Established Names:
LIAISON 1-84 PTH Assay
LIAISON 1-84 PTH Control Set
LIAISON 1-84 PTH Calibration Verifiers

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1545
   21 CFR 862.1660

2. Classification:

   Class II
   Class I, reserved

3. Product code:

   CEW
   JJX

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:
   The DiaSorin LIAISON 1-84 PTH Assay is an *in vitro* chemiluminescent immunoassay (CLIA) intended for the quantitative determination of parathyroid hormone (1-84) in human serum and EDTA plasma. Measurements of parathyroid hormone levels are used in the differential diagnosis of hypercalcemia and hypocalcemia resulting from disorders of calcium metabolism. The test has to be performed on the LIAISON® Analyzer family.

   The DiaSorin LIAISON 1-84 PTH Control Set is intended for *in vitro* diagnostic use as assayed quality control samples to monitor the accuracy and precision of the LIAISON 1-84 PTH Assay.

   The DiaSorin LIAISON 1-84 PTH Calibration Verifiers are assayed quality control materials intended for in vitro diagnostic use in the quantitative verification of calibration and reportable range of the LIAISON 1-84 PTH Assay.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   For use on the LIAISON Analyzer

I. Device Description:

1. LIAISON 1-84 PTH Reagent Integral contains the following components:
   - Magnetic particles - coated with goat polyclonal antibody against 1-84 PTH, stabilizers and preservatives; 2.4 mL.
   - Conjugate -Goat polyclonal antibody conjugated to an isoluminol derivative, with PBS, BSA and preservatives; 12 mL.
   - Assay buffer – phosphate buffer containing BSA, blockers and preservatives; 25 mL.
   - Calibrators, 2 Levels, containing equine serum, synthetic 1-84 PTH at 2 different concentrations, stabilizers and preservatives; 2 vials each level; lyophilized.

2. LIAISON 1-84 PTH Control Set contains:
2 levels of controls containing human plasma spiked with 1-84 PTH, stabilizers and preservatives; 4 vials each level; lyophilized. The target values of the controls are listed below:

Level 1: 30 pg/mL
Level 2: 260 pg/mL

3. LIAISON 1-84 PTH Calibration Verifier Set contains:
4 levels of pooled human plasma spiked with 1-84 PTH with preservative, 1 vial each level, lyophilized. The target values of the calibration verifiers are listed below:

Level 1: 10 pg/mL
Level 2: 80 pg/mL
Level 3: 400 pg/mL
Level 4: 1450 pg/mL

The Calibration Verifier Set and Control Set package insert labeling includes the following disclaimer:

Each serum/plasma donor unit used in the preparation of this product has been tested by a U.S. FDA approved method and found non-reactive for the presence of the antibody to Human Immunodeficiency Virus 1 and 2 (HIV 1/2), the Hepatitis B surface antigen (HBsAg), and the antibody to Hepatitis C (HCV). While these methods are highly accurate, they do not guarantee that all infected units will be detected. This product may also contain other human source diseases for which there is no approved test.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Scantibodies Laboratory, Inc., Whole PTH (1-84) Specific
DiaSorin LIAISON N-TACT PTH Control Set
DiaSorin LIAISON N-TACT PTH Calibration Verifiers

2. Predicate 510(k) number(s):
k001411
k033426
k093498

3. Comparison with predicate:

LIAISON® 1-84 PTH Assay

Similarities		
Item	Candidate Device LIAISON® 1-84 PTH Assay	Predicate Device Whole PTH (1-84) Specific (k001411)
Intended Use	Intended for the in vitro quantitative determination of parathyroid hormone (1-84) in human serum.	Same
Antibody	Goat polyclonal	Same

Differences		
Item	Device LIAISON® 1-84 PTH Assay	Predicate Whole PTH (1-84) Specific (k001411)
Methodology	Chemiluminescent Immunoassay	Immunoradiometric assay
Sample type	EDTA Plasma and Serum	EDTA Plasma
Measuring range	4.0 - 1880 pg/mL	0-2300 pg/mL
Reference range	EDTA plasma: 5.72-45.4 pg/mL Serum: 5.68-47.8 pg/mL	5.0- 39 pg/mL

LIAISON® 1-84 PTH Control Set

Similarities and Differences		
Item	Candidate Device LIAISON® 1-84 PTH Control Set	Predicate Device DiaSorin LIAISON N-TACT PTH Control Set (k033426)
Intended Use	Intended for use as assayed quality control samples to monitor the accuracy and precision of the PTH assay.	Same
Storage	Store at 2-8^{o}C	Same
Levels	2 levels: lyophilized	Same
Concentration	Level 1: 30 pg/mL Level 2: 260 pg/mL	Level 1: 60 pg/mL Level 2: 560 pg/mL

LIAISON® 1-84 PTH Calibration Verifiers

Similarities and Differences		
Item	Candidate Device LIAISON® 1-84 PTH Calibration Verifiers	Predicate Device DiaSorin LIAISON N-TACT PTH Calibration Verifiers (k093498)
Intended Use	Assayed quality control materials intended for the quantitative verification of calibration and reportable range of the PTH assay.	Same
Storage	Store at 2-8^{o} C	Same
Levels	4 levels: lyophilized	Same
Concentration	Level 1:10 pg/mL Level 2: 80 pg/mL Level 3:400 pg/mL Level 4:1450 pg/mL	Level 1:20 pg/mL Level 2:150 pg/mL Level 3: 350 pg/mL Level 4:1500 pg/mL

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

CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition

CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP7-A2, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition

CLSI EP9-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition

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

CLSI C28-A3, How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition

L. Test Principle:

The LIAISON 1-84 PTH assay is a modified two-step, two-site sandwich assay that uses two polyclonal antibodies for capture and detection of the 1-84 PTH molecule. The assay uses 150 µL of human serum or EDTA plasma incubated with and isoluminol conjugated polyclonal antibody with high specificity for the N-terminus of the 1-84 peptide. Following incubation, paramagnetic particles coated with a second polyclonal antibody that binds to the C-terminal region of the 1-84 molecule are added to the reaction and incubated. The design of these antibodies is intended to detect the whole intact 1-84 PTH with no cross reactivity to fragments such as the 7-84 PTH fragment. After the second incubation, the unbound material is removed with a wash cycle. The starter reagents are then added and a flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as relative light units (RLU) and is proportional to the concentration of 1-84 PTH present in the calibrators, controls or samples.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A twenty day reproducibility precision study was performed at DiaSorin Inc. A coded panel comprised of 7 frozen EDTA plasma samples spanning the assay range, and the 2 levels of LIAISON 1-84 PTH controls (lyophilized human plasma) were tested using two reagent lots, in two replicates per run, 2 runs per day for 20 days on one LIAISON Analyzer for a total of 160 replicate results per sample. The 20 day results are summarized for the combined reagent lot numbers below:

		Between-lot		Total	
Sample n=160	Mean PTH (pg/mL)	SD	%CV	SD	%CV
Control1	30.2	1.02	3.4%	1.52	5.0 %
Control 2	305.6	9.86	3.2%	14.08	4.6 %
EDTA 1	11.8	0.37	3.2%	1.23	10.4%
EDTA 2	18.7	0.78	4.1%	1.45	7.7%
EDTA 3	35.2	0.87	2.5%	2.03	5.8%
EDTA 4	176.5	5.67	3.2%	6.69	3.8%
EDTA 5	399.6	12.56	3.1%	18.2	4.6%
EDTA 6	1124.7	37.89	3.4%	50.62	4.5%
EDTA 7	1743.9	47.97	2.8%	101	5.8%

The two lots of assay reagent demonstrated similar precision results. The precision of one representative lot is summarized in the table below:

Sample n=80	Mean (pg/mL)	Intra-Run		Run-to-Run		Day-to-Day		Total (Within-lot)	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 1	29.5	1.08	3.6%	0.72	2.4%	0.71	2.4%	1.48	5.0%
Control 2	298.7	8.35	2.8%	6.86	2.3%	8.09	2.7%	13.50	4.5%
EDTA 1	11.6	1.27	11.0%	0.00	0.0%	0.46	4.0%	1.24	10.7%
EDTA 2	18.2	1.19	6.5%	0.89	4.9%	0.50	2.8%	1.57	8.6%
EDTA 3	34.5	1.43	4.1%	0.73	2,1%	1.10	3.2%	1.94	5.6%
EDTA 4	172.5	4.68	2.7%	3.04	1.8%	3.79	2.2%	6.74	3.9%
EDTA 5	309.8	10.72	2.7%	8.68	2.2%	2.71	0.7%	14.06	3.6%
EDTA 6	1097.9	27.17	2.5%	39.81	3.6%	15.65	1.4%	50.68	4.6%
EDTA 7	1710.0	47.11	2.8%	77.24	4.5%	23.45	1.4%	93.46	5.5%

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b. Linearity/assay reportable range:

One sample pool of each sample type, serum and EDTA plasma, was spiked with PTH 1-84 to achieve PTH levels above the measuring range of the assay and then was diluted with a low patient sample of the same sample type to obtain intermediate PTH concentrations. The low sample was further diluted with specimen diluent which contains no PTH to levels near the claimed LoQ of the assay. Each of the resulting 19 concentrations, ranging from 0.3-2044 pg/mL for EDTA and 0.2- 1802 pg/mL for serum, were analyzed by the LIAISON 1-84 PTH Assay in replicates of three. The results were analyzed by a regression of observed mean PTH concentration versus expected PTH concentration. The resulting equations for each sample type are shown below:

Serum: $y= 0.9992 x - 0.0835$, $R^2= 0.9976$

EDTA plasma: $y= 0.9679 x – 3.328$, $R^2 = 0.9971$

The linearity results for both serum and EDTA plasma support the claimed measuring range of this assay (4.0-1800 pg/mL).

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

Traceability:

The LIAISON 1-84 PTH Calibrators and Calibration Verifiers concentrations are traceable to an in-house standard preparation containing synthetic human PTH (1-84).

Stability:

LIAISON 1-84 PTH Kit Calibrators: A real-time stability study determined the shelf life of the lyophilized LIAISON 1-84 PTH kit calibrators to be 18 months when stored at 2-8°C. Stability studies demonstrated that the open-vial stability of the reconstituted LIAISON 1-84 PTH calibrators is 2 hours at room temperature and onboard the analyzer. The sponsor indicated in the labeling that the calibrators should be stored frozen at -20°C if not used within 2 hours after reconstitution. The LIAISON 1-84 PTH kit calibrators are stable for 8 weeks when stored frozen at -20°C and can be used though 1 freeze-thaw cycle. The stability study protocol and the acceptance criteria have been found acceptable.

LIAISON 1-84 PTH Calibration Verifiers: A real-time stability study determined the shelf life of the LIAISON 1-84 PTH Calibration Verifiers to be 6 months when stored at 2-8°C. A real-time study to determine shelf-life is ongoing. Open-vial stability of the reconstituted LIAISON 1-84 calibration verifiers is 2 hours at room temperature and onboard the analyzer. The sponsor indicated in the labeling that the calibration verifiers should be stored frozen at -20°C if not used within 2 hours after reconstitution. They are stable for 14 days at -20 °C and can be used through one freeze-thaw cycle. The stability study protocol and acceptance criteria were reviewed and found to be acceptable.

LIAISON 1-84 PTH Control Set: The shelf life of the LIAISON 1-84 PTH Control Set is 6 months when stored at 2-8°C as determined by real-time shelf life stability studies. Stability studies demonstrated that the open-vial stability of the reconstituted LIAISON 1-84 PTH Control Set is 2 hours when stored at room temperature. The sponsor indicated in the labeling that the calibrators should be stored frozen at -20°C if not used within 2 hours after reconstitution. Controls are stable for 8 weeks when stored at -20°C and can be used though 1 freeze-thaw cycle. The stability study protocol and the acceptance criteria have been found acceptable.

Value Assignment:

LIAISON 1-84 PTH Kit Calibrators: A minimum of 5 vials of each level of calibrator are tested on a minimum of 3 LIAISON Analyzers, using 2 different LIAISON 1-84 PTH assay kit lots, in a minimum of 5 assay runs with 6 replicates per vial resulting in a minimum of 30 individual replicate results per calibrator level. The calibrator values must fall within a pre-specified range and the target value is lot specific. An example calibrator lot has the following target values::

Calibrator 1: 33.2 pg/mL
Calibrator 2: 1340 pg/mL

LIAISON 1-84 PTH Controls: A minimum of 10 vials of each level of control are tested on a minimum of 3 LIAISON Analyzers, using 2 different LIAISON 1-84 PTH Assay kit lots, in a minimum of 5 assay runs over 10 days with 4 replicates per vial

resulting in a minimum of 40 individual replicate results per control. The mean, standard deviation and %CV for each level of kit control is calculated and the median value must be within 5% of the calculated mean. The controls have the following target values for PTH (1-84) and control range is established using the mean ±2SD:

Control level 1: Mean = 30 pg/mL, control range: 21.0-39.0 pg/mL; Control level 2: Mean = 260 pg/mL, control range: 198-322 pg/mL

LIAISON 1-84 PTH Calibration Verifiers: A minimum of 12 vials of each level of calibration verifier are tested on a minimum of 4 LIAISON Analyzers, using 2 different approved LIAISON 1-84 PTH assay kit lots, in a minimum of 6 assay runs with four replicates per vial resulting in a minimum of 48 individual replicate results. The calibrator verifiers have the following target values for PTH (1-84) and the verifier range is established using the mean ±2SD:

Cal verifier A: Mean = 10 pg/mL, range: 7.00 -13.0 pg/mL
Cal verifier B: Mean = 80 pg/mL, range: 56.0 - 104 pg/mL
Cal verifier C: Mean = 400 pg/mL, range: 304 -496 pg/mL
Cal verifier D: Mean = 1450 pg/mL, range: 1218-1682 pg/mL

d. Detection limit:

Limit of Blank (LoB):
Five blank samples, consisting of 1-84 Calibrator matrix (charcoal stripped horse serum) were tested with the LIAISON 1-84 PTH Assay on two analyzers, with two reagent lots and two operators over six runs (2 replicates/sample/run) on three days for a total of 60 results per reagent lot. The equation used for the determination of LoB is as follows: LoB = μ (blank dose) + 1.653* σ (blank dose)
The LoB is 0.3 pg/mL

Limit of Detection (LoD):
Four human EDTA plasma samples and four human serum samples in the range of the mean LoB to 4 times the mean LoB were tested with the LIAISON 1-84 PTH Assay on two analyzers, with two reagent lots and two operators over six runs (2 replicates/sample/run) on three days for a total of 96 results per sample type. LoD was calculated for both serum and plasma samples for each of the 2 reagent lots using the following equation:
LoD = μ (blank dose) + 1.653* σ (blank dose) * σ (sample Dose)
The LoD for EDTA plasma samples is 1.6 pg/mL. The LoD for serum samples is 0.80 pg/mL.

Limit of Quantitation (LoQ):
Nine human EDTA plasma samples and nine human serum samples in the range of 0.3 to 12 pg/mL were tested with the LIAISON 1-84 PTH Assay on two analyzers, with two reagent lots and two operators over six runs (2 replicates/sample/run) on three days for a total of 144 results per sample type. LoQ value was determined

based on a fitted curve where concentration of PTH has a %CV of 20%. The LoQ for EDTA plasma samples is 3.4 pg/mL. The LoQ for serum samples is 0.84 pg/mL.

The limit of detection and limit of quantitation results for EDTA plasma and serum are summarized in the table below:

Sample type	LoD	LoQ
EDTA Plasma	1.6 pg/mL	3.4 pg/mL
Serum	0.80 pg/mL	0.84 pg/mL

The sponsor is claiming the following assay detection limits for both EDTA plasma and serum samples:

LoB	LoD	LoQ
0.5 pg/mL	1.7 pg/mL	4.0 pg/mL

The claimed measuring range of the assay for both sample types is 4.0 - 1880 pg/mL

e. *Analytical specificity:*

An interference study was performed based on CLSI EP7-A2 guideline to assess common or known substances that could interfere with the measurement of PTH. The potential interferents listed below were spiked into two human EDTA plasma samples with 1-84 PTH concentrations of 40 pg/mL and 70 pg/mL. The two sets of matched spiked and unspiked samples were tested in 12 replicates with one lot of reagent. Significant interference was defined as greater or equal to ±10% difference from the expected concentration. The interference study results are summarized in the following table:

Potential Interferent	Highest Tested Concentration at which no significant interference (≤±10%) was observed
Bilirubin, conjugated	40 mg/dL
Bilirubin, unconjugated	20 mg/dL
Hemoglobin	500 mg/dL
Triglycerides	3000 mg/dL
Cholesterol	500 mg/dL
Albumin	12 g/dL
HAMA	4088 ng/mL
Rheumatoid factor	5380 IU/mL
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Salicylic Acid	60 mg/dL
Ibuprofen	50 mg/dL
Biotin	0.1 µg/dL

Alendronate	8 mg/dL
Etidronate	105 mg/dL
Pamidronate	18 mg/dL
Risedronat	6 mg/dL
Vitamin D2	240 ng/mL
Vitamin D3	240 ng/mL
Calcitrol	1 ng/mL
Alfacalcidol	2.5 ug/mL
Calcium Acetate	40 mg/dL
Magnesium Chloride	40 mg/dL
Aluminum Sulfate	40 mg/dL
Lanthanum Chloride	40 mg/dL
Doxycycline	34.6 µg/mL
Lisinopril	32.7 µg/dL

The assay package insert labeling states the following: Grossly hemolyzed or lipemic samples should not be tested.

Cross reactivity study: Testing was performed to assess the cross-reactivity of the LIAISON 1-84 PTH Assay with other PTH fragments as well as structurally similar proteins. Potential cross reactants, each at a concentration of 200,000 pg/mL, were spiked into LIAISON1-84 PTH Specimen Diluent (horse serum-based zero sample) and tested. The PTH fragments were tested in triplicate using one lot of reagent; and the calcitonin, osteocalcin, and C-telopeptide cross-reactants were tested in quadruplicate with a different kit lot of the assay. The equation used to calculate % cross reactivity is as follows:

$$\frac{\text{(Mean conc. of spiked sample - Mean conc. of the original sample)}}{\text{Spiked Concentrations}} \times 100$$

The following table summarizes the cross-reactivity of PTH fragments and structurally similar proteins with the LIAISON 1-84 PTH assay:

Substance	Spiked concentration	% Cross Reactivity
hPTH 7-84	200,000 pg/mL	0.00105%
hPTH 1-34	200,000 pg/mL	0.00005%
hPTH 13-34	200,000 pg/mL	0.00020%
hPTH 39-68	200,000 pg/mL	0.00090%
hPTH 44-68	200,000 pg/mL	0.00055%
hPTH 39-84	200,000 pg/mL	0.00050%
Calcitonin	200,000 pg/mL	0.00008%
Osteocalcin	200,000 pg/mL	0.00005%
C-Telopeptide (β-crosslaps)	200,000 pg/mL	0.00001%

Hook Effect Study: Testing was performed to determine if the LIAISON 1-84 PTH Assay is susceptible to falsely low results in the presence of very high levels of PTH. Three serum and 3 EDTA plasma samples were spiked with 1-84 PTH equal to several concentrations above the assay measuring range of 1800 pg/mL. The spiked samples were run in triplicate. No high dose hook effect was observed at 1-84 PTH concentrations measured up to 60,000 pg/mL.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed following CLSI EP9-A3. The samples tested consisted of 186 native EDTA plasma samples and 7 spiked samples for a total of 193 samples. The mean of duplicate results for the comparator assay, Scantibodies Laboratory Whole PTH (1-84) Specific, and singlicate results for the LIAISON 1-84 PTH Assay were compared. Passing and Bablok linear regression analyses were performed and the following results were obtained:

LIASON 1-84 PTH Assay vs. Scantibodies Laboratory Whole PTH (1-84) Specific

n	Slope	95% CI	Intercept	95% CI	r	Result range (pg/mL)
193	0.9810	0.9497-1.0204	-2.23	-5.29 to -0.61	0.9812	6.3-1707

b. Matrix comparison:

A matrix comparison study was performed on 188 matched human sample sets of EDTA plasma and serum. A total of 8 samples were spiked in order to span the claimed measuring range. Each sample type was tested in singlicate using one reagent lot. The matrix comparison analysis resulted in the following equation:

$y=1.05x + 0.14$ (y = serum, x= EDTA plasma), $R^2 = 0.9981$

The study supports EDTA plasma and serum sample types for use with the LIAISON 1-84 PTH assay.

The sponsor includes the following limitation regarding sample type in the assay

package insert: "The type of specimen used (serum or EDTA plasma) may influence PTH measurements. During routine monitoring of PTH levels, use the same specimen type throughout the monitoring period to avoid bias in the results."

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):

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   To establish the expected reference range for the LIAISON 1-84 PTH assay, matched pairs of EDTA plasma and serum samples from 125 apparently healthy adults, comprised of 91 females and 34 males, ages 21-70 years old were tested. Subjects tested had normal concentrations of 25OH vitamin D, TSH, total calcium, phosphorus, magnesium, creatinine, and alkaline phosphatase. The Reference range for the LIAISON 1-84 PTH was determined from 125 EDTA samples (91 females and 34 males) and 124 serum samples (90 females and 34 males). Based on the parametric method with 95% reference limit, the following reference range values were established:

Sample type	N	Median PTH (pg/mL)	Observed Range 2.5th to 97.5th Percentile
EDTA plasma	125	25.0	5.72-45.4 pg/mL
Serum	124	25.2	5.68-47.8 pg/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.