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

A. 510(k) Number:

k161158

B. Purpose for Submission:

Modification of antibody source (new goats)

C. Measurand:

Intact Parathyroid Hormone (PTH)

D. Type of Test:

Quantitative, Chemiluminescent Magnetic Particle Immunoassay

E. Applicant:

Immunodiagnostic Systems, LTD

F. Proprietary and Established Names:

IDS-iSYS Intact PTH^N assay

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1545, Parathyroid hormone test system

2. Classification:

   Class II

3. Product code:

   CEW

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The IDS-iSYS Intact PTH^N assay is an in vitro diagnostic device intended for the quantitative determination of intact PTH in human serum or plasma on the IDS-iSYS Multi- Discipline Automated System. Results are to be used in the differential diagnosis of hypercalcemia and hypocalcemia resulting from disorders of calcium metabolism.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   IDS-iSYS Multi-Discipline Automated System

I. Device Description:

IDS-iSYS Intact PTH^N Kit consists of a reagent cartridge and kit calibrators.

The reagent cartridge contains the following:

- Magnetic particles coated with streptavidin in a phosphate buffer containing sodium azide as preservative (<0.1%), 1 bottle, 2.7 mL.
- Conjugate: Anti-PTH (13-34) labelled with an acridinium ester derivative, in buffer containing goat serum with sodium azide as preservative (<0.1%), 1 bottle, 7.25 mL.
- Anti-PTH (39-34) labeled with biotin, in buffer containing bovine and goat proteins with sodium azide as preservative (<0.1%), 1 bottle, 13 mL.

The Kit Calibrators, CAL A and CAL B, consists of a lyophilized porcine serum matrix buffer containing PTH at 2 concentration levels and sodium azide as preservative >1% (w/w%), 1 mL. The Kit Calibrators were cleared in k103325.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   IDS-iSYS Intact PTH

2. Predicate 510(k) number(s):
   k103325

3. Comparison with predicate:

Similarities		
Item	Candidate Device IDS-iSYS Intact PTH^{N}	Predicate Device IDS-iSYS Intact PTH (k103325)
Intended Use	For the quantitative determination of PTH in human serum or plasma.	Same
Assay method	Chemiluminescence immunoassay	Same
Antibody	Goat polyclonal Anti-PTH (39-84) Anti-PTH (13-34)	Same
Sample matrix	Serum and Plasma (K2-EDTA, lithium heparin)	Same
Calibrator	2 levels included in kit	Same

Differences		
Item	Candidate Device IDS-iSYS Intact PTH^{N}	Predicate Device IDS-iSYS Intact PTH (k103325)
Antibody Source	New goats to replace the original (expired) goats as the 1-34 polyclonal antibody source.	Original goats, polyclonal
Reference interval	10.3 to 80.5 pg/mL	11.5 to 78.4 pg/mL
Measuring range	5 to 3500 pg/mL	5 to 5000 pg/mL
Calibration interval	15 days	21 days

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

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Methods; Approved Guideline-Third Edition.

CLSI EP06-A, Evaluation of Linearity of Quantitative Measurement Procedures; A Statistical Approach, Approved Guideline.

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

CLSI EP09-A3, Method 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-Second Edition.

CLSI EP28-A3, How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition.

CEN 13640, In Vitro Diagnostics Medical Devices; Evaluation of Stability of In Vitro Diagnostics Reagent; January 01, 2013.

L. Test Principle:

A chemiluminescent immunoassay technique is used, in which a polyclonal goat anti-human antibody recognizing the C-terminal region (amino acids 39-84) of human PTH is used as the capture antibody. A polyclonal goat anti-human PTH antibody which recognizes the N-terminal region (amino acids1-84) of PTH, is conjugated with acridinium for detection. This system also detects the large PTH fragment of amino acid 7-84. Patient samples are incubated with both antibodies followed by the addition of streptavidin coated magnetic particles with further incubation. A magnet is then used to capture the labeled antibody-antigen complexes, and following a wash and the addition of reagent, the concentration of PTH is determined. Concentration of PTH is directly proportional the amount of emitted light from the acridinium labels.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision was evaluated by testing 1 human serum sample and 6 human K2-EDTA plasma samples using two lots of IDS-iSYS Intact PTH^N reagent cartridges on two analyzers (one lot per analyzer). Each sample was tested in duplicate, 2 runs per day, for 20 days for a total of 80 results per reagent lot/analyzer. Similar precision results were obtained from both lots. Precision results from one lot are provided below:

			Within-run		Total	
Sample	N	Mean (pg/mL)	SD	CV%	SD	CV%
Serum 1	80	15.4	0.5	6.1	1.0	6.7
EDTA plasma 1	80	17.9	1.8	9.9	1.8	9.9
EDTA plasma 2	80	73.7	1.3	1.7	2.3	3.2
EDTA plasma 3	80	337.9	5.1	1.5	6.2	1.8
EDTA plasma 4	80	765.1	13.7	1.8	16.4	2.1
EDTA plasma 5	80	1376.6	20.4	1.5	40.7	3.0
EDTA plasma 6	80	2229.1	35.2	1.6	58.6	2.6

b. *Linearity/assay reportable range:*

Linearity studies were performed using serum and K2-EDTA plasma samples in accordance with CLSI EP-6A.

The serum samples were prepared by diluting a high serum sample with a low serum sample to obtain 15 evenly spaced intermediate PTH sample concentrations. The expected PTH concentrations were as follows: 3.54, 7.28, 11.02, 22.24, 78.35, 115.75, 227.96, 377.58, 751.62, 1125.67, 1499.71, 1873.76, 2247.80, 2621.84, 2743.98, 2995.89, and 3369.93 pg/mL. Each sample was assayed in replicates of four. The following linear regression analysis for serum was obtained:

$y= 1.02 x – 0.2$ pg/mL , $R^2= 1.00$

The K2-EDTA plasma samples were prepared by diluting a high K2-EDTA sample with a low K2-EDTA sample to obtain 15 evenly spaced intermediate PTH sample concentrations. The expected concentrations were as follows: 2.91, 6.31, 9.72, 19.92, 70.96, 104.99, 207.07, 343.18, 683.45, 1023.73, 1364.00, 1704.27, 2044.54, 2384.81, 2725.08, 3065.36, and 3405.63 pg/mL. Each sample was assayed in replicates of four. The following linear regression analysis for K2-EDTA was obtained:

$y= 0.96 x – 0.1$ pg/mL, $R^2= 1.00$

The results from the linearity study support the sponsor's claimed measuring range for the IDS iSYS Intact PTH^N assay of 5.0 to 3500 pg/mL.

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

Traceability:

Cleared in k103325.

Stability:

Cleared in k103325. The calibrators are stable for 6 months unopened when stored at 2-8^o C; for 14 days when open and reconstituted and stored at 2-8^o C; and for 2 hours on board the analyzer.

Calibrator Value Assignment:

Cleared in k103325.

d. Detection limit:

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined in accordance with CLSI EP17-A.

The LoB was determined for three lots of reagent cartridges by testing a zero serum based calibrator in replicates of 10 over 6 assays for a total of 60 measurements per lot. LoB was determined by the parametric method of calculating the concentration corresponding to the 95% probability of detecting a blank sample using the equation LoB= mean $_{(blank)}$ + 1.65 x SD ($_{blank}$).

The LoD was determined for three cartridge reagent lots by assaying 10 serum samples with very low PTH concentrations in duplicate over 6 assays spanning multiple days for a total of 120 measurements per lot. LoD was calculated using a parametric method to determine the lowest concentration that can be detected 95% of the time.

The LoQ was determined for three reagent cartridge lots by testing 10 low PTH level serum samples in duplicate over 6 assays spanning multiple days for a total of 120 measurements per lot. LoQ was determined as the lowest PTH concentration from the regression curve for which %CV is less than 20%.

The results of detection limit studies are summarized in the table below:

Limit of Blank	Limit of Detection	Limit of Quantitation
0.9 pg/mL	2.3 pg/mL	4.5 pg/mL

The claimed measuring range of the assay is 5.0 to 3500 pg/mL.

e. Analytical specificity:

Interference studies were performed in accordance with CLSI EP7-A2. Samples with low and high PTH concentrations were spiked with potential interfering substances. Percent interference was calculated using the following formula:

$$\frac{\text{mean conc. of spiked sample} - \text{mean conc. of un-spiked sample}}{\text{mean concentration of un-spiked sample}} \times 100$$

For total cholesterol and Rheumatoid factor (Rf) the interference was evaluated by recovery of Intact PTH from a high pool was spiked into a sample with known interferent substance levels. Percent recovery was calculated using the formula below:

% Recovery = (Recovery value / Expected recovery value) x 100

The sponsor defines significant interference as a bias in results of ≥ 10%.

The interference study results are summarized in the table below:

Substance	PTH concentrations tested (pg/mL)	Highest concentration tested at which no significant interference was observed
Bilirubin, conjugated	33.7, 1906.7	22 mg/dL
Bilirubin, unconjugated	25, 1700	40 mg/dL
Biotin	22.5, 1818.9	300 nmol/L
Cholesterol	17, 20, 29, 117, 964, 1057	395 mg/dL
HAMA	13, 1900	1000 ng/mL
Hemoglobin	7.6, 2901.2	500 mg/dL
Rheumatoid Factor	445.2, 890.4	1836 IU/mL
Total Protein	16.3, 36.2	10 g/dL
Triglycerides	24.4, 1889.3	3000 mg/dL
Acetaminophen	23.1, 1723.8	200 µg/mL
Carbamazepine	24, 1626.2	200 µg/mL
Ibuprofen	32.4, 3091.1	500 µg/mL

The labeling includes the following limitations:

"Total cholesterol at concentrations greater than 395 mg/dL have been shown to cause falsely elevated Intact PTH results when measured by this assy. Samples that contain high levels of total cholesterol should not be measured using this Intact PTH assay."

"HAMA at concentrations of 1000 ng/mL have been shown to interfere with Intact PTH results when measured by this assay of up to 14.4% bias."

Cross Reactivity:

Cross-reactivity studies were performed according to CLSI EP-7A2. A serum sample and a zero calibrator matrix was spiked with human PTH fragments and structurally similar proteins at the concentrations listed below. The cross reactivity was determined by the following formula:

% cross reactivity =

$$\frac{\text{Mean conc. of spiked sample} - \text{mean conc. of un-spiked sample}}{\text{Spike concentration}} \times 100\%$$

The cross-reactivity of substances with the IDS iSYS Intact PTH assay are summarized below:

Potential cross-reactant	Concentration tested (pg/mL)	Cross-reactivity
PTH (1-84)	2000	100%
PTH (7-84)	2000	83.6%
PTH (1-34)	100,000	<0.01%
PTH (39-84)	100,000	<0.01%
PTH (53-84	100,000	<0.01%
PTH (39-68)	100,000	<0.01%
Human Calcitonin	100,000	<0.01%
CTX-1 (β Cross Laps)	100,000	<0.01%
Osteocalcin	100,000	<0.01%

High Dose Hook Effect:

A hook effect study was performed to determine if the IDS-iSYS Intact PTH^{N} assay is susceptible to produce falsely low results in the presence of very high levels of PTH. One K2-EDTA sample and two serum samples were spiked with the following concentrations of 1-84 PTH: 5,000, 25,000, 50,000, 75,000, and 100,000 pg/mL. Each specimen was measured in replicates of 4 using 3 reagent lots. The study demonstrated that no high dose hook effect was observed for intact PTH concentrations up to 100,000 pg/mL.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The IDS iSYS Intact PTH^{N} assay was compared against the previously cleared IDS iSYS Intact PTH (k103325) assay in accordance with CLSI EP-9A2.

A total of 312 serum samples (291 native, 21 spiked) were assayed with the candidate and predicate devices at two external sites. The PTH concentrations as measured by the candidate device ranged from 6.3 to 3378 pg/mL. Three reagent cartridge lots of the candidate device were used in the study. Deming regression analysis of the results yielded the following regression equation:

y=1.02x – 0.7, r=1.00 (n=312)

b. Matrix comparison:

A matrix comparison study was performed on 52 matched (45 native, 7 spiked) sample sets of serum, serum separator tube (SST) serum, K2-EDTA plasma, and Lithium-heparin plasma. The sample range tested was between 10.6 and 2759.0 pg/mL. Passing-Bablok regression analysis was performed on the comparative data. The following regression analyses were obtained:

K2-EDTA plasma vs.	Slope	Intercept	r
Serum	0.94	2.55	1.00
SST serum	0.93	2.38	1.00
Lithium Heparin	0.98	0.42	1.00

The results of the matrix comparison study support the sponsor's claim that K2-EDTA plasma, serum, SST serum and Lithium Heparin plasma are acceptable sample types to use with the IDS iSYS Intact PTH^N assay.

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:

A reference interval study was performed by testing 129 K2-EDTA plasma samples using the IDS iSYS Intact PTH^N assay. The samples were collected from 62 females and 67 males between the ages of 21 to 89 years of age with normal calcium, phosphate, and TSH values. The following reference range, based on the central 95% interval, was obtained:

Intact PTH reference interval: 10.3 to 80.5 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.