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

A. 510(k) Number:

k061190

B. Purpose for Submission:

New device

C. Measurand:

Parathyroid Hormone

D. Type of Test:

Quantitative, Immunoenzymatic assay

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

Access Intact PTH assay

Access Intact PTH Calibrators

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
Parathyroid Hormone (CEW)	Class II	21 CFR 862.1545 Parathyroid hormone test system.	75 Chemistry(CH)

Product Code	Classification	Regulation Section	Panel
Calibrator (JIT)	Class II	21 CFR 862.1150 Secondary calibrator	75 Chemistry(CH)

H. Intended Use:

1. Intended use(s):

   The Access Intact PTH assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of intact parathyroid hormone (parathyrin, PTH) levels in human serum and plasma using the Access Immunoassay Systems. It is indicated to aid in the differential diagnosis of hyperparathyroidism, hypoparathyroidism, or hypercalcemia of malignancy and can be used intraoperatively. Assay results should be used in conjunction with clinical data to assist the clinician in making individual patient management decisions.

   The Access Intact PTH calibrators are intended to calibrate the Access Intact PTH assay for the quantitative determination of intact parathyroid hormone levels in human serum and plasma using the Access Immunoassay Systems.

2. Indication(s) for use:

   See Intended Use above

3. Special conditions for use statement(s):

   Prescription use only

4. Special instrument requirements:

   The Access Intact PTH and Access Intact PTH calibrator is intended to use with the Access Immunoassay Systems.

I. Device Description:

The Access Intact PTH reagent consists of a dual chambered reagent pack containing three ready-to-use-liquid reagents as follows:

- R1a: Paramagnetic particles coated with goat anti-PTH antibody suspended in TRIS buffered saline with bovine serum albumin (BSA), surfactant, and < 0.1% sodium azide.
- R1b: TRIS buffered saline with block ACE, protein (mouse, goat), surfactant, and < 0.1% sodium azide.
- R1c: Mouse monoclonal anti-PTH alkaline phosphatase conjugate in ACES buffered saline with BSA, surfactant, and < 0.1% sodium azide.

The Access Intact calibrator kit contains six vials of different concentrations of synthetic Intact PTH.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Elecsys Parathyroid Hormone Test System and DPC Immulite Turbo PTH

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

   k992680, k053533

3. Comparison with predicate:

Similarities for Routine Intact PTH		
Item	Access PTH	Predicate (Roche Elecsys PTH)
Intended Use	The Access Intact PTH assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of intact parathyroid hormone (parathyrin, PTH) levels in human serum and plasma using the Access Immunoassay Systems. It is indicated to aid in the differential diagnosis of hyperparathyroidism, hypoparathyroidism, or hypercalcemia of malignancy and can be used intraoperatively. Assay results should be used in conjunction with other clinical data to assist the clinician in making individual patient management decisions.	Immunoassay for the *in vitro* quantitative determination of intact parathyroid hormone in human serum and plasma for the differential diagnosis of hypercalcemia and hypocalcemia.
Assay Principles	The Access Intact PTH assay is a two-site immunoenzymatic ("sandwich") assay.	Electrochemiluminescence immunoassay employing the sandwich principle
Solid Support	Paramagnetic particles coated with goat anti-PTH.	Streptavidin coated microparticles
Detection System	Utilizes dioxetane-based chemiluminescent substrate; Measures light production from a chemiluminescent reaction.	Chemiluminescent emission
Sample types	Serum and plasma	Serum and plasma

Differences for Routine Intact PTH		
Item	Access PTH	Predicate (Roche Elecsys PTH)
Calibrator	Six levels (0, ~10, ~60, ~300, ~1500, and ~3500 pg/mL) of synthetic PTH antigen in a buffered protein solution with preservatives.	2 point calibration and master curve provided via the reagent barcode.
Reportable range	1-3500 pg/mL	1.2-5000 pg/mL
Functional sensitivity	4 pg/mL	6 pg/mL
Reference intervals	12-88 pg/mL	15-65 pg/mL

Similarities for Intra-operative PTH		
Item	Access Intra-operative PTH	Predicate (DPC Turbo PTH-Intraoperative)
Intended Use	The Access Intact PTH assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of intact parathyroid hormone (parathyrin, PTH) levels in human serum and plasma using the Access Immunoassay Systems. It is indicated to aid in the differential diagnosis of hyperparathyroidism, hypoparathyroidism, or hypercalcemia of malignancy and can be used intraoperatively.	For in vitro diagnostic use with the IMMULITE and IMMULITE 1000 analyzers- for the quantitative measurement of intact parathyroid hormone (parathyrin, PTH) in EDTA plasma or serum. It is intended as an aid in the differential diagnosis of hypercalcemia and hypocalcemia and can be used intraoperatively.
Assay Principles	The Access Intact PTH assay is a two-site immunoenzymatic ("sandwich") assay.	Solid phase, chemiluminescent immunometric assay.
Solid Support	Paramagnetic particles coated with goat anti-PTH.	Bead coated with affinity purified goat polyclonal anti-PTH (44-84) antibody.
Detection System	Utilizes dioxetane-based chemiluminescent substrate; Measures light production from a chemiluminescent reaction.	Chemiluminescent emission.
Sample types	Serum and plasma	Serum and plasma

Differences for Intra-operative PTH		
Item	Device	Predicate (DPC Turbo PTH-Intraoperative)
Calibrator	Six levels (0, ~10, ~60, ~300, ~1500, and ~3500 pg/mL) of synthetic PTH antigen in a buffered protein solution with preservatives.	Intact PTH adjustors (Low and High) of lyophilized synthetic human intact PTH in a buffered matrix.

Differences for Intra-operative PTH		
Item	Device	Predicate (DPC Turbo PTH-Intraoperative)
Reportable range	6-3500 pg/mL	4-2500 pg/mL
Reference interval	12-88 pg/mL	8-74 pg/mL

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

STANDARDS
Title and Reference Number
CSLI Guideline, EP5-A *Evaluation of Precision Performance of Clinical Chemistry Devices* CSLI Guideline, EP7-A *Interference Testing in Clinical Chemistry; Approved Guideline*
Other Standards
EN ISO 17511: 2003, *Metrological Traceability of Values Assigned to Calibrator and Control Materials.*

L. Test Principle:

The Access Intact PTH assay is a two-site immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel, along with a monoclonal anti-PTH antibody conjugated to alkaline phosphatase, TRIS buffered saline with proteins and paramagnetic particles coated with a goat polyclonal anti-PTH antibody. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of PTH in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision studies:

   Precision was evaluated according to CLSI EP5-A protocol. The method consisted of assaying three EDTA plasma patient samples in replicates of two, for 20 runs in both the routine and intraoperative modes. The mean of the replicates, standard deviation, and the percent CV for within run, between run and total precision were determined by analysis of variance (ANOVA). The Access Intact PTH assay exhibits total imprecision of $\leq 8\%$ CV at

concentrations > 12 pg/mL for the routine mode and ≤12% CV at concentrations > 12 pg/mL for the intraoperative mode. All 3 lots of reagents tested meet the total imprecision claim. These results meet the applicant's design specifications for precision of ≤ 8% CV at concentrations greater than 10 pg/mL for the routine mode and precision of ≤ 15% CV for concentrations between 10-50 pg/mL and ≤ 10% CV for higher concentrations for the intraoperative mode.

b. *Linearity/assay reportable range:*

For the Routine PTH mode:

Dilution recovery studies for the Access Intact PTH assay were completed using the Access 2 platform using the routine mode. Six EDTA plasma samples range from 356 to 3185 pg/mL were diluted using sample diluent A. Three samples were spiked with synthetic PTH in order to obtain the high values needed for this study. Eight dilutions were prepared for each sample and tested in replicates of 8 for the neat sample and replicates of 4 for each dilution. Assay range from 4.6 to 3185 pg/mL were tested and found to have a mean % recovery ranged from 91% to 103% for the routine mode. Studies showed that all 6 samples tested were within the design specification for slope of 1.00 ± 0.1.

For the Intraoperative PTH mode:

Dilution recovery studies for the Access Intraoperative PTH assay were completed using the Access 2 platform using the intraoperative mode. Six EDTA plasma samples range from 502 to 3084 pg/mL were diluted using sample diluent A. Three samples were spiked with synthetic PTH in order to obtain the high values needed for this study. Eight dilutions were prepared for each sample and tested in replicates of 8 for the neat sample and replicates of 4 for each dilution. Assay range from 6.3 to 3054 pg/mL were tested and found to have a mean % recovery ranged from 85% to 98% for the routine mode. Studies showed that all 6 samples tested were within the design specification for slope of 1.00 ± 0.1.

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

Traceability:

The Access Intact PTH calibrator is traceable to the manufacturer's working calibrators. The average recovery of WHO standard preparation material 79/500 diluted in Sample Diluent A (Cat. No. 81908) is 57% for the Routine Mode and 53% for the Intraoperative Mode range of the assay. The traceability process is based on EN ISO 17511: 2003, *Metrological Traceability of Values Assigned to Calibrator and Control Materials*.

Value assignments and verification processes for Access PTH calibrators are done using an internal protocol. Access Intact PTH calibrators are used for both the routine mode and the intraoperative mode.

Stability:

Long term (shelf life) stability of the calibrators was performed by running controls and patient samples at time 0,1,3,6, and 9 months intervals. Stability studies are continuing at this time. The recommended temperature storage for lyophilized calibrators is 2-10^{0}C. The mean value for each sample at each time period was compared to the mean value of that control on day zero and compared to the expected range. All controls values fall into the assigned range. Open vial (in use) stability was performed by running four samples at time 0,1,2,4,6,8.5,25, and 50 hours intervals. Reconstituted calibrators were stored at the recommended storage conditions of either 18-25°C or 2-10°C. At each time point, the reconstituted calibrators were used to generate a new calibration curve and four quality control samples were assayed in replicates of two on an Access 2 instrument using the routine mode. The mean value for each control level at each time period is compared to the mean value of that control on day zero and compared to the expected range. All control values fall into the assigned range. The data supports reconstituted calibrator open vial stability 2 hours if stored at 18-25°C or 10 hours if stored at 2-10°C.

d. *Detection limit:*

The Limit of Detection determination was based on multiple measurements of the Intact PTH calibrator, S0, on multiple instruments. The mean, SD, and % CV were calculated. The lowest detectable level of PTH distinguishable from zero with 95% confidence is 0.102 pg/mL for the routine mode and 0.368 pg/mL for the intraoperative mode. The applicant chose the analytical sensitivity of 1 pg/mL for the routine mode and 6 pg/mL for the intraoperative mode.

e. *Analytical specificity:*

The specificity of the PTH assay was evaluated as described in CSLI EP7-A Guidelines. Substances tested are listed below and were found not to interfere (< 10% bias).

Interfering Substances Summary: Routine Mode				
Substance Added	Concentration Added	Expected (pg/mL)	Observed (pg/mL)	Mean % Interference
Triolein	3000 mg/dl	52.2	54.7	4.8
Bilirubin	20 mg/dL	54.9	53.6	-2.5
Conjugated Bilirubin	20 mg/dL	53.5	51.8	-3.2
Cholesterol	500 mg/dL	51.2	50.7	-1.1
Acetaminophen	20 mg/dL	53.2	53.3	0.2
Human Serum Albumin	15 g/L	54.8	51.8	-5.6
Hemoglobin	500 mg/dL	49.6	51.7	4.3
Pamidronate	10 µg/mL	54.3	54.6	0.6
Propofol	2 µg/mL	54.1	53.4	-1.3
D Biotin	100 µg/L	54.6	54.5	0.0
Salicylic acid	50 mg/dL	52.8	53.8	1.9
Ibuprophen	40 mg/dL	53.4	52.3	-2.2
Heparin	8000 IU/dL	53.9	53.9	0.0

Cross reactivity studies were performed and the results are as follows:

Potential Cross Reactants		
Substance Added	Concentration Added pg/mL (pmol/L)	% Cross-Reactivity
PTH (1-84)	4713 (500)	100
PTH (7-84)	4391 (500)	72
PTH (44-68)	5672 (2000)	<0.1%
PTH (53-84)	7022 (2000)	<0.1%
PTH (39-84)	9970 (2000)	<0.1%
PTHrp(1-34)	8036 (2000)	<0.1%

Limitations to the procedure:

The applicant states that for assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interferes with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. The applicant recommends to carefully evaluate the results of patients suspected of having these antibodies.

f. *Assay cut-off:*

NA

2. Comparison studies:

a. *Method comparison with predicate device*

For the Routine PTH mode: A total of 500 EDTA plasma samples were evaluated using two different Access Immunoassay systems and Roche Elecsys (predicate) analyzers at external and internal laboratories in Europe. Deming regression analyses were used to evaluate the correlations between results obtained using the Access PTH assay and the Roche Elecsys (predicate) assay. The methods comparison analyses demonstrated acceptable agreement between Access Intact PTH assay results and Roche Elecsys PTH assay results. All comparisons met acceptance criteria for slope (1.0 ± 0.10) and Pearson correlations ($r \geq 0.95$). Correlation of Roche Elecsys PTH versus Access PTH showed a regression of $y = 1.0914 \, x -11.479$, y = Access PTH, and x = Roche Elecsys PTH. Range of observations = 16-2627 pg/mL, r = 0.99.

For the Intraoperative PTH mode: A total of 400 EDTA plasma samples were evaluated using Access 2 system and DPC Immulite 1000 Turbo PTH (predicate) analyzers at an external site in Europe. Deming regression analyses were used to evaluate the correlations between results obtained using the Access Intraoperative PTH mode and the DPC Immulite 1000 Turbo PTH (predicate) assay. The methods comparison analyses demonstrated acceptable agreement between Access Intact PTH assay results and DPC Immulite 1000 Turbo PTH assay results. Agreement between the predicate and Access Intraoperative PTH assay was acceptable with the Pearson regressions of $r \geq 0.95$.

Correlation of Access Intraoperative PTH verses the DPC Immulite 1000 Turbo PTH showed a regression of $y = 0.8695 \, x + 0.13$, y = Access PTH, and x = DPC Immulite 1000 Turbo PTH. Range of observations = 8-2453 pg/mL, r = 0.996.

b. *Method comparison between the Access Intact PTH routine mode and intraoperative mode:*

A total of 493 EDTA plasma samples were evaluated using the Access Intact PTH assay routine mode and the intraoperative mode on the Access Immunoassay system. Deming regression analyses were used to evaluate the correlations between results obtained using the Access PTH routine mode and the intraoperative mode. The methods comparison analyses demonstrated acceptable agreement between Access Intact PTH routine mode and intraoperative mode.

Correlation of Access PTH routine mode verses the intraoperative mode showed a regression of y = 0.94 x + 9.69, y = Access PTH intraoperative mode, and x = Access PTH routine mode. Range of observations = 13-2848 pg/mL, r =1.00. Comparisons met acceptance criteria for slope (1.0± 0.10) and Pearson correlations (r ≥ 0.95).

c. *Matrix comparison:*

A comparison study was performed using 50 matched serum and plasma (EDTA and heparin) samples across the range with doses up to ~ 2000 pg/mL. Samples were run as replicates of 4 on the Access system using both the routine and intraoperative mode. For statistical analysis, a linear regression including the slope, intercept, and correlation coefficient were calculated. The slope differences met the sponsor's design specification, which requires the difference between plasma (EDTA, heparin) and serum samples to be ≤ 10% for both the routine and intraoperative modes. Results are presented in the tables below:

Sample Type Comparison Summary-Routine Mode				
Comparison	Slope (95% confidence interval)	Intercept (95% confidence interval)	r	n
Heparin vs. EDTA	1.059 (1.049, 1.070)	0.843 (-3.871, 5.557)	0.999	50
Serum vs. EDTA	1.036 (1.023, 1.049)	3.705 (-2.202, 9.612)	0.999	50

Sample Type Comparison Summary-Intraoperative Mode				
Comparison	Slope (95% Confidence Interval)	Intercept (95% Confidence Interval)	r	n
Heparin vs. EDTA	1.037 (1.026, 1.047)	1.001 (-4.512, 6.514)	0.999	50
Serum vs. EDTA	1.037 (1.0279, 1.0461)	2.143 (-2.468, 6.753)	0.999	50

d. *Method Comparison: Access Systems Cross-Platform*

To verify the equivalence of the Access platform family members with respect to the Access PTH assay, a method comparison study was performed. Ten EDTA plasma patient samples with PTH concentrations ranged from approximately 8 to 3000 pg/mL were tested in replicates of four, in 5 different

runs, for a period of 5 days, on each of the Access platforms in both the routine and intraoperative modes. Below are the paired platform instruments comparisons:

1. Access 2 vs. Access

2. UniCel DxL 800 vs. Access

3. UniCel DxL 800 vs. Access 2

The LXi Synchron 725 and UniCel DxC 600i incorporate an Access 2 system and are represented by the Access 2 in this correlation study.

The results are shown in the table below:

Platform Verification Method Comparison-Routine Mode			
	Access (x) vs Access 2 (y)	Access (x) vs Dxl (y)	Access 2 (x) vs Dxl (y)
Slope	0.9461	1.0421	1.0998
(95% Confidence Interval)	(0.933, 0.959)	(1.027, 1.057)	(1.080, 1.119)
Intercept	16.3104	7.1600	-9.9210
(95% Confidence Interval)	(3.851, 29.770)	(-6.482, 20.802)	(-27.438, 7.596)

Platform Verification Method Comparison-Intraoperative Mode			
	Access (x) vs Access 2 (y)	Access (x) vs Dxl (y)	Access 2 (x) vs Dxl (y)
Slope	0.9601	1.0051	1.0466
(95% Confidence Interval)	(0.952, 0.968)	(0.992, 1.018)	(1.032, 1.061)
Intercept	8.1717	-5.4108	-13.8177
(95% Confidence Interval)	(0.516, 16.860)	(-19.190, -8.369)	(-28.717, 1.081)

3. Clinical studies:

   a. *Clinical Sensitivity:*
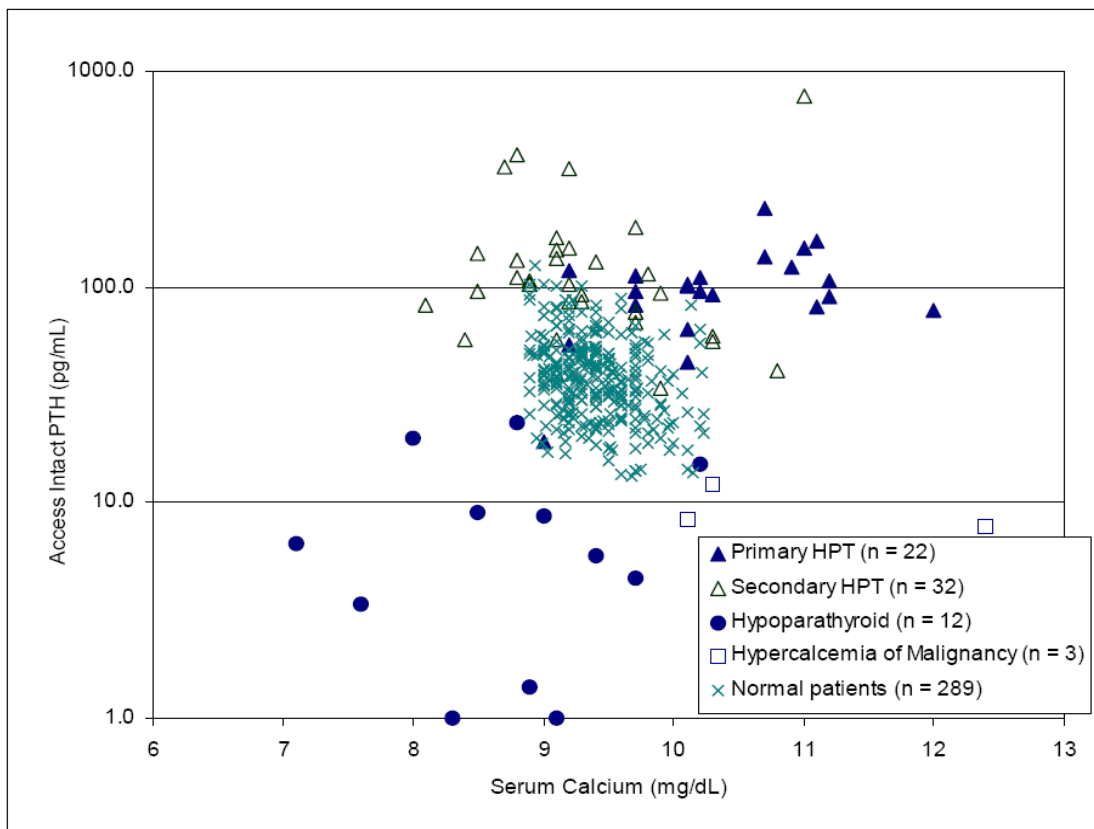   Not applicable

   b. *Clinical specificity:*
       Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Pathological sample evaluation was performed by measuring Intact PTH in apparently healthy individuals and patients with following disorders of calcium metabolism: primary hyperparathyroidism, secondary hyperparathyroidism, hypoparathyroidism, and hypercalcemia of malignancy. The mean PTH result was plotted vs. the mean Calcium result for each disorder. Results were summarized in the graph below. The results below reflect a typical profile for the pathological samples and were in alignment with the literature. (Marx, S. NEJM 2000:343:1863-1875, Hyperparathyroid and Hypoparathyroid Disorders)

Pathological Samples

Calcium vs. Access Intact PTH

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Reference range were established by using 289 matched human EDTA plasma and serum samples from apparently healthy male and female subjects aged 19-67 years, samples were tested in duplicate. Results were analyzed to generate a 95% non-parametric lower and upper reference limit for each sample type. Results are summarized in the table below:

Access Intact PTH Reference Range Summary

Sample Type	N	Median Age	Age Range	Reference Interval (pg/mL)
Serum	289	40	19-67	12-87
EDTA Plasma	289	40	19-67	15-88

Access Intraoperative Intact PTH Reference Range Summary

Sample Type	N	Median Age	Age Range	Reference Interval (pg/mL)
Serum	289	40	19-67	12-94
EDTA Plasma	289	40	19-67	16-96

A non-parametric Wilcoxon signed-ranks test was used to compare the EDTA plasma and serum sample populations. The 2-tailed p was 0.1719 indicating that there is no statistically significant difference between the sample types. The applicant chose 12-88 pg/mL to be the reference range for both serum and plasma, and for both routine and intraoperative mode of Access Intact PTH.

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.