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

A. 510(k) Number:

k121981

B. Purpose for Submission:

New device

C. Measurand:

Intact Parathyroid Hormone (PTH)

D. Type of Test:

Quantitative, two-site sandwich immunoassay using direct chemiluminometric technology

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

ADVIA® Centaur Intact Parathyroid (iPTH) Assay

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CEW	Class II	21 CFR 862.1545 Parathyroid Hormone Test System	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for Use below

2. Indication(s) for use:

   The ADVIA Centaur iPTH assay is for *in vitro* diagnostic use in the quantitative determination of intact parathyroid hormone (iPTH) in EDTA plasma or serum using the ADVIA Centaur XP system. This assay is intended to be used as an aid in the differential diagnosis of hyperparathyroidism and hypoparathyroidism.

3. Special conditions for use statement(s):

   For *in vitro* diagnostic use only

4. Special instrument requirements:

   ADVIA Centaur XP system

I. Device Description:

The ADVIA Centaur iPTH reagents come in two configurations:

- 5 ReadyPack© primary reagent packs containing ADVIA Centaur© iPTH Lite Reagent and Solid Phase Reagent (500 tests)
- 1 ReadyPack© primary reagent packs containing ADVIA Centaur© iPTH Lite Reagent and Solid Phase Reagent (100 tests)

The ReadyPack consists of the following:

Lite Reagent 5.0 mL/reagent pack:

The Lite Reagent contains acridium ester-labeled polyclonal goat antihuman PTH (1-34 N-terminal) antibody (~ 1µg/mL) in phosphate buffered saline with goat IgG, bovine gamma globulin, bovine serum albumin, and preservatives

Solid Phase 20.0 mL/reagent pack:

The Solid Phase reagent contains biotinylated polyclonal goat anti-human PTH (39-84 region) antibody (~3µg/mL) and streptavidin (~0.4 mg/mL) covalently coupled to paramagnetic latex particles in phosphate buffered saline with goat IgG, bovine gamma globulin, bovine serum albumin, and preservatives.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Abbott Architect Intact PTH Assay

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

k063232

3. Comparison with predicate:

Similarities		
Item	Candidate Device ADVIA® Centaur Intact Parathyroid Hormone (iPTH) Assay	Predicate Device Architect Intact PTH Assay k063232
Intended Use	For in vitro diagnostic use in the quantitative determination of intact parathyroid hormone (iPTH) in plasma or serum	Same
Measurement	Quantitative	Same
Operating Principle	Sandwich Immunoassay	Same
Technology	Chemiluminescence	Same
Sample Type	EDTA Plasma, Serum	Serum and Plasma
Sample volume	200 µL	150 µL
Calibration	2 point	6 Point
Detection Antibody	Goat polyclonal antibody conjugated to Acridium Ester in the Lite Reagent	Goat polyclonal antibody
Expected Values	14-85 pg/mL	8.7-77.1 pg/mL
Assay Range	5.5– 1900 pg/mL	3.0-3000 pg/mL (Routine) 4.0-2500 pg/mL (STAT)
Interference	No significant interference by hemolysis, icterus, lipemia, or biotin at tested levels	No significant interference by hemolysis, icterus, lipemia, at tested levels
Capture Antibody	Goat polyclonal antibody conjugated to biotin. Biotin conjugate is directly coupled to streptavidin magnetic particle in the Solid Phase reagent.	Goat polyclonal antibody conjugated to biotin. Biotin conjugate is in solution in the Lite Reagent

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

- CLSI Guideline EP5-A2: Evaluation of Precision Performance of Qualitative Measurement Methods

- CLSI Guideline EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation
- CLSI Guideline EP6-A: Evaluation of the Linearity of Qualitative Measurement Methods

L. Test Principle:

The ADVIA Centaur Intact PTH assay is a two-site sandwich immunoassay using direct chemiluminometric technology. PTH in the sample reacts with the first antibody which is a polyclonal goat anti-human PTH (N-terminal 1-34) antibody labeled with acridinium ester. This complex is then captured by the solid phase (a second antibody which is a biotinylated polyclonal goat anti-human PTH (39-84 region) antibody that is preformed to streptavidin coated paramagnetic latex particles). Unbound materials are then removed by washing. Acid Reagent and Base Reagent are then added to initiate the chemiluminescent reaction. A direct relationship exists between the amount of PTH present in the patient sample and the amount of relative light units (RLUs) detected by the system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision was evaluated following CLSI guideline EP5-A2. Two replicates of each of 11samples, to include 6 EDTA plasma pools from patients, 2 calibrators and 3 levels of commercial control materials, were assayed in duplicate over the course of 20 days, on 2 instruments using 2 lots of reagent, two runs per day, for a total of 40 runs and 80 replicates. A representative lot is summarized below:

   Precision Study Results

					Within run		Total	
Sample	Mean PTH Conc. (pg/mL)	No. of days	No. of Runs	N	SD	% CV	SD	%CV
Pool 1	16.7	20	40	80	0.8	4.6	1.5	9.2
Low Calibrator	33.0	20	40	80	2.0	6.0	2.3	6.9
Control 1	45.2	20	40	80	2.0	4.4	3.2	7.0
Pool 2	47.3	20	40	80	1.4	2.9	2.3	4.8
Pool 3	97.3	20	40	80	2.8	2.9	3.9	4.0
Pool 4	175.6	20	40	80	4.8	2.7	10.5	6.0
Control 2	196.6	20	40	80	6.8	3.5	8.3	4.2
Control 3	691.0	20	40	80	17.8	2.6	24.5	3.5
Pool 5	699.8	20	40	80	20.1	2.9	24.4	3.5
High Calibrator	807.7	20	40	80	23.1	2.9	37.7	4.7
Medical Decision Pool 5	1802.9	20	40	80	46.7	2.6	57.7	3.2

b. Linearity/assay reportable range:

Fourteen (14) levels of linearity samples spanning the assay range were prepared by dilutions of a high EDTA plasma pool (~2200 pg/ml) with iPTH diluent (buffered goat serum with no analyte). The sample range tested was 5.5 pg/mL-2173.4 pg/mL.

Linearity was evaluated following CLSI guideline EP6-A. The sponsor chose to perform 1st, 2nd, and 3rd order polynomial regression analysis on each of the dilution series. The first order generates the best linear fit. The linear regression is

Y=1.008x-2.500, R=0.997

Based on linearity results, the sponsor claims that the assay is linear across the reportable range (5.5-1900 pg/mL)

Hook Effect Study

A high dose hook effect study was performed by preparing two high activity iPTH samples and spiking EDTA plasma samples with human PTH. The concentration range was 195-200,000 pg/mL (195, 391, 781, 1563, 3125, 6250, 12500, 25000, 50000, 100000, 200000). A serial two fold dilution was performed using Multi-diluent 11 (buffered goat serum). The neat (undiluted) samples and the diluted samples were assayed on the ADVIA Centaur XP system using two reagent lots. Sponsor states that no hook effect was seen in samples with a concentration up to 200,000 pg/mL iPTH.

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

The ADVIA Centaur Intact PTH assay standardization is maintained with internal standards manufactured using purified human iPTH (1-84); values have been assigned to correlate to a commercially available iPTH assay.

Calibrators and controls were previously cleared in k020217

On-board stability for the ADVIA Centaur Intact PTH assay was established by real time studies on the ADVIA Centaur XP system. The stability study protocol and the acceptance criteria have been found acceptable. The on board stability of the reagent is 28 days with a calibration interval of 14 days. The ADVIA Centaur Intact PTH assay reagent is stable until the date printed on the label when stored at 2-8˚C.

d. Detection limit:

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined following guideline EP17-A.

For LoB determination, 5 replicates of the assay specific diluent, 2 runs per day for five days using 2 ADVIA Centaur XP systems with two reagent lots of ADVIA Centaur iPTH reagents – giving 100 determinations in total.

For LoD determination, 7 low analyte sample pools were each measured in 5 replicates per run, 2 runs per day for 5 days using 2 lots of ADVIA Centaur iPTH reagent for a total of 200 replicates using two ADVIA Centaur XP systems.

For LoQ determination, 7 low analyte sample pools were each measured in 5 replicates per run, 2 runs per day for 5 days using 2 lots of ADVIA Centaur iPTH reagents-giving 200 determinations. The seven low analyte samples were the same used for the LoD study. The level of imprecision used to accept LoQ was less than 20%.

Result Summary

Based on the study results, the following detection limit claims were made:

LoB	LoD	LoQ
1.93 pg/mL	3.44 pg/mL	5.55 pg/mL

The measuring range of the assay is 5.5 – 1900 pg/mL

e. *Analytical specificity:*

Interference

The sponsor evaluated the effect of the interfering substances using three patient serum pools.. Each potential interfering substance was spiked into each of the three serum pools. A control sample was prepared by spiking with the appropriate diluent at the same volume as the interfering substance stock. Interference was defined by the sponsor as ≤ 10% difference from the control sample.

	Highest Concentration Tested that showed no interference
Hemoglobin (red blood cell hemolysate)	500 mg/dL
Triglycerides (Intralipid)	3,000 mg/dL
Bilirubin (conjugated and unconjugated)	40 mg/dL
Biotin	1000 ng/mL

Cross Reactivity

The sponsor evaluated cross-reactivity by using a normal EDTA plasma sample (~40 pg/mL) and the assay specific Multi diluent 11 (control sample). The potential cross reactants were spiked into each matrix and serially diluted with their respective controls that had not been spiked with the cross reactant. The % cross-reactivity was

calculated using the following equation:

%Cross-reactivity=

Dose of test protein sample (pg/mL)-dose of control sample (pg/mL)/concentration of protein tested (pg/mL) X 100

Cross-reactant Tested	Concentration Tested	% Cross-reactivity
PTH (1-34) fragment	300	≤ 2%
PTH (39-68) fragment	100,000	≤ 2%
PTH (39-84) fragment	100,000	≤ 2%
PTH (44-68) fragment	100,000	≤ 2%
PTH (53-84) fragment	100,000	≤ 2%
Calcitonin	100,000	≤ 2%
PTH (7-84) fragment	300	51.4%
Beta-Cross Laps	1,000	≤ 2%
Osteocalcin	50,000	≤ 2%

The sponsor has included a limitation in their labeling which states "The Advia Centaur iPTH assay will detect non-Intact PTH (1-84) such as PTH fragment (7-84). PTH fragment (7-84) may cause falsely elevated Intact PTH results in patients with abnormal renal function because these patients may have various concentrations of PTH fragment (7-84) in their blood. In patients with abnormal renal function, please interpret the Intact PTH result with caution and do not make patient management decisions on the iPTH result alone. A study of characterized PTH fragments is provided in Lopez et al *(Selected Reaction Monitoring-Mass Spectrometric Immunoassay Responsive to Parathyroid Hormone and Related Variants)Clin Chem* 2010;56:281-290.

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

A total of 177 plasma (EDTA) samples (111 renal dialysis patients and 66 non-renal patients) were tested with the ADVIA Centaur iPTH assay and the predicate assay (Abbott Architect Intact PTH (k063232). All samples tested were unaltered native patient samples. Samples were analyzed in singlicate and samples tested ranged from 10.5 pg.mL to 1882 pg/mL.

Results of the Linear Regression Analysis are as follows:

System (y)	N	Regression Equation	R	Sample Range (pg/mL)

ADVIA Centaur iPTH	177	Y=1.03x-3.32	0.991	10.5-1882

Based on the regression analysis result, the sponsor claimed equivalency to the predicate assay.

b. Matrix comparison:

A total of 79 matched natural sample pairs (EDTA plasma and serum) ranging from 11.1 pg/mL to 1791 pg/mL were analyzed on the ADVIA Centaur XP system. All samples tested were unaltered native patient samples. EDTA plasma is considered the primary tube type for this assay. The results are presented in the table below.

	N	Regression Equation	R	Sample Range (pg/mL)
ADVIA Centaur iPTH	79	Y = 0.98x+3.72	0.992	11.2-1791

Based on the data, the sponsor claims EDTA plasma and serum samples are acceptable for this 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):

Not applicable

4. Clinical cut-off**:**

Not applicable

5. Expected values/Reference range:

The reference interval was assessed from 208 paired serum and EDTA plasma samples from healthy donors. Samples were obtained from a commercial source. A total of 180 samples were used for the analysis. 26 samples were excluded from the analysis for out of range calcium (below 8 or above 10.3 mg/dL). Two samples (one serum and one plasma) were removed from the analysis due to no result.

95% of the intact PTH values for the plasma results fell in the range of 13.8-85 pg/mL with an overall range of 11.7 – 100.6 pg/mL. 95% of the intact PTH values for the serum results fell in the range of 12.4 – 76.8 pg/mL with an overall range of 9.1 – 90.3 pg/mL.

Expected Values Summary

Sample Type	N	LL	UL	LL 90% CI	UL 90% CI
Plasma	180	13.8	85.0	11.7 - 15.4	74.6-100.7
Serum	180	12.4	76.8	9.1 – 13.5	59.0-90.3

Based on the results, the expected values for the ADVIA Centaur iPTH assay are 13.8 – 85.0 pg/mL for plasma and 12.4 to 76.8 pg/mL for serum.

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.