DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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May 23, 2017

SIEMENS HEALTHCARE DIAGNOSTICS INC.
DARIUS DARUWALA
SENIOR SPECIALIST, REGULATORY AFFAIRS
511 BENEDICT AVENUE
TARRYTOWN NY 10591

Re: K163658
Trade/Device Name: ADVIA Centaur Intact Parathyroid Hormone (PTH) Assay
Regulation Number: 21 CFR 862.1545
Regulation Name: Parathyroid hormone test system
Regulatory Class: II
Product Code: CEW
Dated: April 24, 2017
Received: April 25, 2017

Dear Darius Daruwala:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kellie B. Kelm -S

for Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k163658

Device Name
ADVIA Centaur® Intact Parathyroid Hormone (PTH) Assay

Indications for Use *(Describe)*
The ADVIA Centaur® Intact Parathyroid Hormone (PTH) assay is for in vitro diagnostic use in the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma using the ADVIA Centaur XP system. This assay is intended to be used to aid in the differential diagnosis of hyperparathyroidism, hypoparathyroidism, or disorders of calcium metabolism. This assay can be used intra-operatively.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary of Safety and Effectiveness

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of 21 CFR 807.92 and the Safe Medical Device Act of 1990.

The assigned 510(k) Number is: K163658

1. Date Prepared

May 22, 2017

2. Applicant Information

Contact: Darius Daruwala
Regulatory Affairs Senior Specialist

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3. Regulatory Information

Table 1. Regulatory Information for ADVIA Centaur PTH Assay

Trade Name	ADVIA Centaur® Intact Parathyroid Hormone (PTH)
Model Numbers	10699154 (1-pack); 10699155 (5-pack)
Common Name	Immunoassay, intact parathyroid hormone
Classification Name	Parathyroid Hormone Test System
FDA Classification	Class II
Review Panel	Clinical Chemistry (75)
Product Code	CEW
Regulation Number	862.1545

4. Predicate Device Information

ADVIA Centaur Intact Parathyroid Hormone (iPTH)

Predicate Device Name: ADVIA Centaur Intact Parathyroid Hormone (iPTH)

510(k) Number: K133601

5. Intended Use / Indications for Use

ADVIA Centaur Intact Parathyroid Hormone (PTH)

The ADVIA Centaur Intact Parathyroid Hormone (PTH) reagent is for *in vitro* diagnostic use in the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma using the ADVIA Centaur XP system.

This assay is intended to be used to aid in the differential diagnosis of hyperparathyroidism, hypoparathyroidism, or disorders of calcium metabolism. This assay can be used intra-operatively.

6. Device Description

Table 2. Summary of Ingredients of the ADVIA Centaur PTH Assay Components

Component	Volume	Ingredients
ADVIA Centaur PTH Primary Reagent ReadyPack (included in assay kit)		
ADVIA Centaur PTH Lite Reagent	10.0 mL/pack	Acridinium ester-labeled mouse monoclonal anti-human PTH antibody (~0.6 mg/L) in buffered saline with mouse gamma globulin, bovine serum albumin, and preservatives
ADVIA Centaur PTH Solid Phase Reagent	20.0 mL/pack	Biotinylated mouse monoclonal anti-human PTH antibody bound to streptavidin-coated paramagnetic particles (~0.4 g/L) in buffered saline with bovine gamma globulin, bovine serum albumin, and preservatives
ADVIA Centaur PTH Calibrator (included in assay kit)		
ADVIA Centaur PTH Low and High Calibrators	1.0 mL/vial	After reconstitution, low or high levels of intact PTH synthetic peptide in buffered saline with human EDTA plasma (10%), surfactants, and preservatives

7. Purpose of the Submission

The purpose of this submission is a premarket notification for a new device: ADVIA Centaur Intact Parathyroid Hormone (PTH) assay.

8. Comparison of Candidate Device and Predicate Device

Table 3. Comparison of ADVIA Centaur PTH Assay to Predicate

Item	ADVIA Centaur Intact Parathyroid Hormone (PTH) Assay (Candidate Device)	ADVIA Centaur Intact Parathyroid Hormone (iPTH) Assay (Predicate Device)
Intended Use	For *in vitro* diagnostic use in the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma using the ADVIA Centaur XP system.	For *in vitro* diagnostic use in the quantitative determination of intact parathyroid hormone (iPTH) in EDTA plasma or serum using the ADVIA Centaur systems.
Indications for Use	This assay is intended to be used to aid in the differential diagnosis of hyperparathyroidism, hypoparathyroidism, or disorders of calcium metabolism. This assay can be used intra-operatively.	This assay is intended to be used to aid in the differential diagnosis of hyperparathyroidism and hypoparathyroidism.
Measurement	Quantitative	Same

Table 3. Comparison of ADVIA Centaur PTH Assay to Predicate

Item	ADVIA Centaur Intact Parathyroid Hormone (PTH) Assay (Candidate Device)	ADVIA Centaur Intact Parathyroid Hormone (iPTH) Assay (Predicate Device)
Methodology	Chemiluminescence	Same
Assay Protocol	Sandwich immunoassay	Same
Traceability/ Standardization	Internal standards. Values have been assigned to correlate to the Predicate device.	Same
Specimen Type	Human serum and plasma	Same
Sample Volume	50 µL	200 µL
Measuring Range	6.3 to 2000 pg/mL	6.3 – 1900 pg/mL
Calibration	2-point calibration	Same
Detection Antibody	Mouse monoclonal antibody conjugated to Acridium Ester in the Lite Reagent	Goat polyclonal antibody conjugated to Acridium Ester in the Lite Reagent
Capture Antibody	Biotinylated mouse monoclonal anti-human PTH antibody with streptavidin-coated paramagnetic particles pre-formed in Solid Phase Reagent	Biotinylated goat polyclonal anti-human PTH antibody with streptavidin-coated paramagnetic particles pre-formed in Solid Phase Reagent
Expected Values	18.4 – 80.1 pg/mL (plasma) 18.5 – 88.0 pg/mL (serum)	13.8 – 85.0 pg/mL (plasma) 12.4 – 76.8 pg/mL (serum)

9. Standard/Guidance Document References

The following recognized standards from Clinical Laboratory Standards Institute (CLSI) were used as a basis of the study procedures described in this submission:

- § Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition (CLSI EP05-A3, 2014; Recognition Number 7-251)
- § Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP06-A, 2003; Recognition Number 7-193)
- § Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition (CLSI EP07-A2, 2005; Recognition Number 7-127)
- § Measurement Procedure Comparison And Bias Estimation Using Patient Samples -- Third Edition (CLSI EP9-A3, 2013; Recognition Number 7-245)
- § Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline -- Second Edition (CLSI EP17-A2, 2013; Recognition Number 7-233)
- § Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition (CLSI EP28-A3c – formerly C28-A3c, 2010; Recognition Number 7-224)
- § Medical devices – Application of risk management to medical devices (ANSI/AAMI/ISO 14971:2007/(R)2010; Recognition Number 5-70)

10. Performance Characteristics: ADVIA Centaur PTH

10.1 Precision

A 20-day precision study was performed according to CLSI EP5-A2. Six EDTA plasma samples and three levels of controls were tested.

Sample	Mean		Repeatability (Within-Run)			Within-Lab (Total Precision)		
	(pg/mL)	(pmol/L)	SD (pg/mL)	SD (pmol/L)	% CV	SD (pg/mL)	SD (pmol/L)	% CV
Sample 1	16.9	1.79	0.9	0.09	5.16	1.1	0.12	6.78
Sample 2	50.3	5.34	1.4	0.15	2.78	2.3	0.24	4.57
Sample 3	146.4	15.52	1.9	0.20	1.30	2.9	0.30	1.95
Sample 4	409.2	43.37	6.8	0.72	1.67	16.9	1.79	4.13
Sample 5	596.3	63.20	7.3	0.78	1.23	9.7	1.02	1.62
Sample 6	1080.4	114.52	11.8	1.25	1.09	25.1	2.66	2.32
ADVIA Centaur PTH Quality Controls								
Control 1	41.6	4.41	0.4	0.04	0.91	1.4	0.15	3.36
Control 2	235.9	25.00	1.9	0.20	0.81	4.4	0.46	1.85
Control 3	874.0	92.64	8.0	0.85	0.92	18.4	1.96	2.11

10.2 Linearity

A linearity study was performed according to CLSI EP06-A using 11 serially diluted samples spanning the assay range. The mean was taken from each sample tested in triplicate. As presented below, the bias from the linear fit estimate was <10%. The assay is linear from 6.3 to 2000 pg/mL.

Sample	Expected Dose (pg/mL)	Observed Dose (pg/mL)	Recovery (Observed vs Expected)	Weighted Linear Fit Estimate	Deviation from Linear Fit
A	2.7	2.7	100%	2.6	3%
B	3.8	3.5	92%	3.7	-4%
C	7.1	6.6	93%	6.8	-4%
D	20.3	19.2	95%	19.5	-1%
E	73.3	68.9	94%	70.2	-2%
F	143.9	137.0	95%	137.8	-1%
G	285.1	264.3	93%	273.0	-3%
H	567.5	529.9	93%	543.4	-3%
I	850.0	819.8	96%	813.9	1%
J	1132.4	1089.9	96%	1084.3	1%
K	2262.1	2262.1	100%	2166.0	4%

10.3 Dilution Recovery

A low sample pool (~ 22 pg/mL PTH) was spiked with a commercially available synthetic PTH peptide to reach levels of approximately 3,000 pg/mL (318 pmol/L), 6,000 pg/mL (636 pmol/L) and 9,000 pg/mL (954 pmol/L). Each sample was diluted 1:5 with ADVIA Centaur Multi-Diluent 13 on-board the ADVIA Centaur XP system. All samples were run in triplicate.

Sample	Observed Mean (pg/mL)	Expected (pg/mL)	Observed Mean (pmol/L)	Expected (pmol/L)	Recovery (%)
1	3068.8	3020.9	325.3	320.2	101.6
2	6270.8	6019.8	664.7	638.1	104.2
3	9253.2	9018.7	980.8	956.0	102.6
Mean					**102.8**

10.4 Method Comparison

Method Comparison studies were done with 349 EDTA plasma patient samples distributed over the assay range to demonstrate equivalence to the Predicate (ADVIA Centaur iPTH). The ADVIA Centaur PTH assay shows good correlation in sample results compared to the Predicate. The regression equation from the analysis is presented below.

ADVIA Centaur PTH = 1.02(iPTH) – 2.18 pg/mL (r = 0.99)

10.5 Matrix Comparison

The ADVIA Centaur PTH assay was evaluated using different specimen matrices and tube collection types. A specimen collection study was performed using 56 matched specimens drawn in different tube types including serum red top, serum separator tube (SST), EDTA, lithium heparin, and sodium heparin, on two reagent lots. No significant difference between tube types was observed. The following results were obtained:

Comparison[a]	Regression Equation	r
Serum vs. Dipotassium EDTA plasma	Serum = 0.99 EDTA – 1.85	0.996
Serum separator tube vs. Dipotassium EDTA plasma	Serum separator tube = 1.03 EDTA + 0.20	0.996
Lithium Heparin vs. Dipotassium EDTA plasma	Lithium Heparin = 0.99 EDTA + 1.95	0.998
Sodium Heparin vs. Dipotassium EDTA plasma	Sodium Heparin = 1.00 EDTA + 1.03	0.997

[a] This study was performed using Becton Dickinson tubes. Siemens recommends that laboratories evaluate performance when using other manufacturers' tubes.

10.6 Reference Intervals

Reference intervals for the ADVIA Centaur PTH assay were established according to CLSI EP28-A3c. A total of one hundred forty-two (142) paired serum and EDTA plasma samples from apparently healthy donors were analyzed. Based on a 95% confidence interval, the following reference intervals were established.

Sample Type	Lower Limit (95% CI)	Upper Limit (95% CI)
EDTA Plasma	18.4 pg/mL	80.1 pg/mL
Serum	18.5 pg/mL	88.0 pg/mL

10.7 Detection Limit

The limit of blank (LoB), limit of detection (LoD), and the limit of quantitation (LoQ) were determined as described in CLSI protocol EP17-A2. The LoB is defined as the highest measurement result that is likely to be observed for a blank sample. The LoD is defined as the lowest concentration of PTH that can be detected with 95% probability. The LoQ is defined as the lowest concentration of PTH that can be detected at a total CV of 20%.

The ADVIA Centaur PTH assay has a LoB of 1.5 pg/mL, a LoD of 3.2 pg/mL, and a LoQ of 4.6 pg/mL.

10.8 Interference

Interference studies were performed according to CLSI EP07-A2. Two EDTA sample pools were tested. One sample pool had approximately 75 pg/mL PTH. The second sample pool had approximately 600 pg/mL PTH. These sample pools were spiked with potential interferents. There was no indication of interference ($\leq$ 10% effect) up to the interferent levels claimed. Results are presented below.

Endogenous Substance	Endogenous Substance Concentration	Interference (%)
Hemoglobin	500 mg/dL	-4.5
Triglycerides	3275 mg/dL	-0.4
Bilirubin (unconjugated)	60 mg/dL	-2.2
Bilirubin (conjugated)	60 mg/dL	5.9
Biotin	1000 ng/mL	6.9
Cholesterol	500 mg/dL	-6.5
Total Protein (high)	12 g/dL	-4.2
Total Protein (low)	6 g/dL	-7.5
IgG	6 g/dL	1.3
Calcitrol	360 pg/mL	2.5
Furosemide	181 µmol/L	-2.6
Caffeine	308 µmol/L	2.3
Aliskiren	200 µg/mL	5.3
Enalaprilat	0.86 µmol/L	-2.6
Epoetin alfa	15 mU/L	-1.2
Fosrenol	20 ng/mL	3.4

Six human plasma samples containing human anti-mouse antibodies (HAMA) were tested at 2 PTH concentrations. Samples at a PTH concentration of 60 pg/mL (6.36 pmol/L) demonstrated a difference of -11.5% to 3.2% from the expected values. Samples at a PTH concentration of 340 pg/mL (36.04 pmol/L) demonstrated a difference of -3.8% to 2.4% from the expected values.

10.9 Cross-Reactivity

Cross reactivity was evaluated in the ADVIA Centaur iPTH immunoassay using a normal human EDTA plasma sample and blank assay diluent for each test compound. An aliquot of

each sample was spiked with test compound so that the final test sample contained the compound at the required concentration. A second aliquot of the base pool is spiked with just the diluent to serve as a control sample. Multiple replicates of the test and control samples are processed. Cross-reactivity was calculated as the % difference between the mean test and control sample results, with respect to the test compound concentration. Results are presented below.

Cross-Reactant (Conc.)	Normal Patient (pg/mL)		Blank (MD13) (pg/mL)	
Calcitonin (100,000 pg/mL)	Test	30.39	Test	0.34
	Control	30.33	Control	0.00
	%XR	**0.0001%**	**%XR**	**0.0003%**
Beta-CrossLaps (10,000 pg/mL)	Test	30.40	Test	0.00
	Control	31.15	Control	0.00
	%XR	**-0.0075%**	**%XR**	**0.0000%**
Osteocalcin (50,000 pg/mL)	Test	30.56	Test	0.00
	Control	30.71	Control	0.00
	%XR	**-0.0003%**	**%XR**	**0.0000%**
PTH (1-34) (12,000 pg/mL)	Test	30.87	Test	0.00
	Control	30.79	Control	0.00
	%XR	**0.0007%**	**%XR**	**0.0000%**
PTH (39-68) (100,000 pg/mL)	Test	30.66	Test	0.00
	Control	30.69	Control	0.00
	%XR	**0.0000%**	**%XR**	**0.0000%**
PTH (53-84) (100,000 pg/mL)	Test	29.81	Test	0.00
	Control	30.74	Control	0.00
	%XR	**-0.0009%**	**%XR**	**0.0000%**
PTH (44-68) (100,000 pg/mL)	Test	30.57	Test	0.00
	Control	30.24	Control	0.00
	%XR	**0.0003%**	**%XR**	**0.0000%**
PTH (39-84) (100,000 pg/mL)	Test	30.24	Test	0.00
	Control	29.82	Control	0.00
	%XR	**0.0004%**	**%XR**	**0.0000%**
PTH-RP (1-34) (100,000 pg/mL)	Test	30.13	Test	0.00
	Control	29.95	Control	0.00
	%XR	**0.0002%**	**%XR**	**0.0000%**
PTH (7-84) (300 pg/mL)	Test	141.94	Test	52.51
	Control	29.85	Control	0.00
	%XR	**37.36%**	**%XR**	**17.5033%**

10.10 High-Dose Hook Effect

Patient samples with high intact PTH levels can cause a paradoxical decrease in the RLUs (high-dose hook effect). In this assay, patient samples with intact PTH levels as high as 100,000 pg/mL (10,600 pmol/L) are reported as > 2000 pg/mL (> 212 pmol/L).

10.11 Stability

The onboard stability of the ADVIA Centaur PTH reagents is 28 days with a calibration interval of 21 days. Unopened reagents and calibrators are stable until the date printed on the box label when stored at 2-8°C.

10.12 Clinical Study

A clinical study was performed to confirm the effectiveness of the ADVIA Centaur® Intact Parathyroid Hormone (PTH) assay for Intra-operative (IO) use. Sets of specimens from 30 subjects that qualified for the primary endpoints (described below), that met the inclusion criteria, and which were not excluded based on exclusion criteria, were analyzed using the ADVIA Centaur PTH assay on the Centaur XP system.

The following Inclusion/exclusion criteria were used:

Inclusion Criteria

- Patients undergoing parathyroid surgery with intra-operative parathyroid (PTH) testing.
- Patients who have available preoperative calcium and PTH measurements
- Patients who have baseline PTH and PTH monitored on the day of surgery on a clinical PTH test device cleared by the FDA for use intra-operatively.

Exclusion Criteria

- Patients who do not meet inclusion criteria.
- Specimens for which handling and storage guidelines aren't followed.
- Specimens which do not have sufficient quantity available for testing.
- Specimens from pediatric subjects (<21 years old.)

Specimens underwent testing in single replicates on both the ADVIA Centaur XP PTH assay and the comparator (hospital) assays.

For this clinical study, the 'Miami' criterion was utilized to determine 'success'.

> Miami Criterion: A successful surgery is defined to be a 50% or greater drop in PTH level from the greater of the pre-incision or pre-excision baseline values to the 10 minute post-excision test result after the last parathyroid gland excision.

The analyses were based on agreement between the ADVIA Centaur PTH Assay (investigational device) and the assays used by participating surgeons/sites (comparator devices), utilizing the same criteria of a successful surgery for each. Concordance between the surgeon's assays and PTH is presented in the table below.

		PTH Assay Used During Surgery	
		Successful	Unsuccessful
ADVIA Centaur PTH	Successful	29	1*
	Unsuccessful	0	0

The above table displays success based on the Miami criteria for the first 30 set of patient samples that have a 10 minute post-excision draw.

Primary Endpoint Positive Agreement = 29/29 = 100%

Primary Endpoint Overall Agreement = 29/30 = 96.7%

* Note that for one subject, local PTH device did not reach 50% drop from baseline until a blood draw after the 10 minute draw, therefore by the Miami criterion for the surgery is defined as a 'failure'. That subject's specimens yielded only a 48% drop in PTH values by 10 minutes post-excision with the assay used during surgery, but a 55% drop with the ADVIA

Centaur PTH assay run onsite. This was the only set of patient samples that were discrepant based on the Miami criterion definition of success.

11. Conclusions

Based on the results of comparative testing, the new ADVIA Centaur Intact Parathyroid Hormone (PTH) assay is substantially equivalent in principle and performance to the currently-marketed predicate device, the ADVIA Centaur Intact Parathyroid Hormone (iPTH) assay, cleared under 510(k) k133601.