510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K200210

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

ADVIA Centaur® Total hCG assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DHA	Class II	21 CFR 862.1155 - Human Chorionic Gonadotropin (HCG) Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New Device

B Measurand:

Human chorionic gonadotropin (hCG)

C Type of Test:

Quantitative, chemiluminescent immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

For in vitro diagnostic use in the quantitative determination of human chorionic gonadotropin (hCG) in serum or plasma (EDTA or lithium heparin) using the ADVIA Centaur® XP system.

Human chorionic gonadotropin measurements are intended for use as an aid in the early detection of pregnancy.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

ADVIA Centaur XP System.

IV Device/System Characteristics:

A Device Description:

The ADVIA Centaur® Total hCG assay reagents come in two configurations containing either one or five ReadyPack primary reagent pack and ADVIA Centaur Total hCG Master Curve card.

The ReadyPack consists of the following:

ADVIA Centaur ThCG ReadyPack® primary reagent pack; Lite Reagent 5.0 mL/reagent pack polyclonal goat anti-hCG antibody (~0.1 µg/mL) labeled with acridinium ester in buffered saline with sodium azide (0.1%) and preservatives

ADVIA Centaur ThCG ReadyPack primary reagent pack; Solid Phase Reagent 22.5 mL/reagent pack monoclonal mouse anti-hCG antibody (~0.02 mg/mL) covalently coupled to paramagnetic particles in buffered saline with sodium azide (0.1%) and preservatives

ADVIA Centaur ThCG ReadyPack ancillary reagent pack; ThCG Diluent 25.0 mL/reagent pack buffered heat-treated equine serum with EDTA, sodium azide (< 0.1%), and preservatives

ADVIA Centaur ThCG Diluent 50.0 mL/vial buffered heat-treated equine serum with EDTA, sodium azide (< 0.1%), and preservatives

B Principle of Operation:

The ADVIA Centaur® Total hCG (ThCG) assay uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is a polyclonal goat anti-hCG antibody. The second antibody, in the Solid Phase, is a purified monoclonal mouse anti-hCG antibody. These two antibodies are specific for different epitopes that are present on both the free ß-subunit and the ß-subunit of intact hCG.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Atellica IM Total hCG (ThCG)

B Predicate 510(k) Number(s):
K172322

C Comparison with Predicate(s):

Device & Predicate Device(s):	K200210	K172322
Device Trade Name	ADVIA Centaur® Total hCG assay	Atellica IM Total hCG (ThCG) assay
General Device Characteristic Similarities		
Intended Use/Indications For Use	Same	For *in vitro* diagnostic use in the quantitative determination of human chorionic gonadotropin (hCG) in human serum or plasma (EDTA or lithium heparin) as an aid in the early detection of pregnancy.
Measurement	Same	Quantitative
Assay Principle	Same	2-site Sandwich immunoassay
Technology	Same	Direct chemiluminescent
Sample Type	Same	Serum, EDTA Plasma, lithium heparin plasma
Calibration	Same	2-point
General Device Characteristic Differences		
Assay Range	4.0-1000 mIU/mL (IU/L)	2.6–1000 mIU/mL (IU/L)
Sample Volume	50 µL	25 µL
Reagent Volume	100 µL of Lite Reagent and 450 µL of Solid Phase	50 µL of Lite Reagent and 255 µL of Solid Phase
Incubation Time	7.5 minutes at 37°C.	8 minutes at 37°C.

Device & Predicate Device(s):	K200210	K172322
Traceability	The ADVIA Centaur Total hCG assay is traceable to the World Health Organization (WHO) 5th IS 7/364 reference material.	The Atellica IM ThCG assay standardization is traceable to the World Health Organization (WHO) 4th IS 75/589 reference material. Assigned values for calibrators are traceable to this standardization.

VI Standards/Guidance Documents Referenced:

CLSI EP09-A3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition.
CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach.
CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures: Approved Guidelines-Third Edition.
CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, 3rd Edition.
CLSI EP07:Ed3: Interference Testing in Clinical Chemistry; Approved Guideline —Third Edition.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision was evaluated in studies following recommendations in CLSI EP05-A3. Samples were assayed in duplicate in 2 runs per day for 20 days using 2 reagent lots on 2 ADVIA Centaur XP systems. The following results are representative of the performance of the assay:

			Repeatability		Between-Run		Between-Day		Within-Lab	
Sample Type	N	Mean mIU/mL (IU/L)	SD mIU/mL (IU/L)	CV (%)	SD mIU/mL (IU/L)	CV (%)	SD mIU/mL (IU/L)	CV (%)	SD mIU/mL (IU/L)	CV (%)
Serum A	320	6.63	0.29	4.4%	0.09	1.3%	0.24	3.6%	0.39	5.8%
Serum B	320	15.85	0.53	3.3%	0.45	2.8%	0.31	2.0%	0.76	4.8%
Serum C	320	819.28	20.25	2.5%	22.47	2.7%	12.09	1.5%	32.58	4.0%
Control 1	320	7.43	0.30	4.1%	0.15	2.0%	0.32	4.3%	0.46	6.2%
Control 2	320	24.64	0.61	2.5%	0.14	0.6%	0.58	2.3%	0.85	3.5%
Control 3	320	164.66	2.96	1.8%	0.79	0.5%	2.71	1.6%	4.09	2.5%

2. Linearity:

Linearity of the ADVIA Centaur® Total hCG assay was performed following recommendations in CLSI EP06- A guideline. Thirteen (13) samples were prepared by serially diluting a high hCG concentration sample with a low concentration serum sample. The study was performed using one (1) reagent lot and three replicates per level on one ADVIA Centaur XP system. Linearity was evaluated using weighted linear regression. The linearity study included samples spanning hCG concentrations from 1.7 to 1126 mIU/mL.

The expected and recovered hCG were plotted and gave the following linear regression equation:

Observed = 0.99(Expected) + 0.12 mIU/mL

The results from the linearity study support an analytical measuring range from 4.0 mIU/mL to 1000 mIU/mL.

Dilution Recovery

The sponsor provided dilution studies which supported the measurement of samples above 1000 mIU/mL for samples diluted by a factor of 2, 4, 8 or 16.

3. Analytical Specificity/Interference:

Interferences

Interference testing was conducted following recommendations in CLSI EP07 guideline. To test the interferents listed below, two (2) female human serum pools were prepared by spiking a female serum sample pool with a high concentration hCG serum sample pool from a pregnant female to create a low (around 5.0 mIU/mL) and a high (around 500 mIU/mL) concentration level sample pool. These base pools were divided further into two parts for each interferent; a control sample with no interferent present (spiked with interferent vehicle only) and a spiked sample with interferent present. The interferents were tested at multiple concentrations as presented below including a low and/or mid and/or a high-level concentration. Testing was done with two (2) ADVIA Centaur ThCG reagent lots on one (1) ADVIA Centaur XP system with four (4) replicates.

The observed interference effect, *Dobs,* was computed as the difference between the means of the test and control samples.

Dobs = *Interference* = (test sample mean – control sample mean)

To report the level of interferent for a quantitative assay as percent (%) bias, the following calculation was used:
% Bias = [100* Dobs] / [control sample mean]

There was no significant interference (defined by the sponsor as ≤10% bias) up to the concentrations summarized below:

Substance	Highest Substance Concentration tested at which no significant interference was observed
Human Serum Albumin	6 g/dL
Acetaminophen	20 mg/dL
Acetylsalicylic acid	65 mg/dL
Heparin	7200 IU/dL
Ibuprofen	50 mg/dL
EDTA	3.4 µmol/L
Ethanol	600 mg /dL
Atropine	20 mg/dL
Caffeine	556 um/L
Gentisic acid	117 µmol/L
Bilirubin (Conjugated)	40 mg/dL
Bilirubin (Unconjugated)	40 mg/dL
Hemoglobin	1000 mg/dL
Intralipid	3000 mg/dL

Cross-Reactivity

Cross-reactivity testing was performed using two (2) ADVIA Centaur® ThCG reagent lots on one (1) ADVIA Centaur XP system at four hCG concentrations around: 0, 10, 50 and 500 mIU/mL. Measurements were made in four replicates per sample. The cross-reactants were tested at the concentrations listed in the table below.

Cross-Reactant	hCG Result Control Sample (mIU/mL)	hCG Result Spiked Sample (mIU/mL)	% Change
FSH 500 mIU/mL	7.7	8.0	4%
	54.9	54.4	-1%
	493.1	475.4	-4%
TSH 1000 µIU/mL	7.6	7.4	-3%
	54.2	51.6	-5%
	499.9	462.9	-7%
LH 500 mIU/mL	7.8	7.0	-10%
	56.2	47.7	-15%
	487.9	428.5	-12%
hGH 500 ng/mL	7.3	7.2	-2%
	53.0	52.9	0%
	482.3	487.7	1%
PRL 1000 ng/mL	7.9	7.5	-5%
	54.6	54.6	0%
	490.5	494.2	1%

Hook Effect

No high dose hook effect was observed up to 500,000 mIU/mL.

4. Assay Reportable Range:

The assay analytical measuring interval ranges from 4.0 mIU/mL to 1000 mIU/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Traceability

The ADVIA Centaur Total hCG assay is traceable to the World Health Organization WHO 5th IS 7/364 reference material.

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were evaluated to determine detection capabilities using the ADVIA Centaur® XP System according to internal procedure governed by CLSI guideline EP17-A2.

Limit of Blank

LoB testing was performed using two (2) reagent lots on one (1) ADVIA Centaur XP instrument. The study consisted of four (4) blank samples (various diluent pools with no detectable level of hCG) that were tested in 5 replicates per sample, 2 runs per day, and 5 test days for a total of 200 replicates per reagent lot. Results were calculated using two-point calibration stored from first day of testing. The maximum observed LoB across all reagent lots was 1.14 mIU/mL.

Limit of Detection

LoD testing was performed using two (2) reagent lots on one (1) ADVIA Centaur® XP instrument. The study consisted of 10 samples that were tested in 5 replicates per sample per run, 2 runs per day, and 5 test days. Results were calculated using two-point calibration stored from first day of testing.

For each reagent lot, LoD was determined using 694 determinations and an LoB of 1.14 mIU/mL. Using the precision profile protocol, the LoD was determined as the dose at which 95% of the measurements would be greater than the LoB. The highest LoB was used in the calculations of the LoD. The maximum observed LoD across all reagent lots was 1.99 mIU/mL.

Limit of Quantitation

LoQ was determined by testing six human low concentration serum sample pools in the hCG concentration range of 1.4 - 8.2 mIU/mL. Testing was performed on two (2) ADVIA Centaur® reagents lots on one ADVIA Centaur XP system. Each sample was tested in five (5) replicates for ten (10) runs over a period of five (5) days, yielding a total of 300 determinations for each reagent lot. The largest LoQ observed result across all reagent lots tested was 3.9 mIU/mL and the sponsor claimed LoQ is 4.0 mIU/mL. The LoQ study incorporated both precision and a bias component with a 30% error limit.

Detection Capabilities	mIU/mL
LoQ	4.0
LoD	3.0
LoB	2.0

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Method comparison studies were conducted following recommendations in CLSI EP09-A3 guideline. Serum samples were measured in singlicate using one (1) ADVIA Centaur Total hCG reagent lot on one (1) ADVIA Centaur XP system (candidate device) and one (1) Atellica IM ThCG reagent lot on one (1) Atellica IM analyzer (predicate device). A total of 117 serum samples including 12 contrived serum samples were evaluated. The following results were obtained:

y = 0.96 x - 3.0 mIU/mL, Correlation coefficient (r) = 0.997

2. Matrix Comparison:

Serum and plasma (K2 EDTA and lithium heparin) sample equivalence was evaluated by matrix comparison studies by testing matched-sample sets spanning the measurement range of the assay. The studies were conducted following recommendations in CLSI EP09-A3 guideline. The following results were obtained.

Tube (y) vs. Serum (x)	N	Sample Interval	Slope	Intercept	r
Dipotassium EDTA plasma	53	4.7 – 948.9 mIU/mL	0.99	0.3	1.00
Lithium heparin plasma	51	4.7 – 975.7 mIU/mL	1.01	- 0.3	1.00

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable

2. Clinical Specificity:

   Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):
   Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The reference range study was performed following recommendations in CLSI EP28-A3c guideline. The following results were obtained:

Sample Category	N	Median (mIU/mL) (IU/L)	Reference Interval mIU/mL) (IU/L) 2.5-97.5 Percentile
Non-Pregnant Females (Age: ≤40)	130	0.03	0.03 – 0.6
Post-menopausal Females (Age: ≥41)	150	0.02	0.02 – 2.9

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.