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

A. 510(k) Number:

k172322

B. Purpose for Submission:

Adding previously cleared assay to the Atellica IM Test System

C. Measurand:

Total beta human chorionic gonadotropin (β-hCG) in human serum

D. Type of Test:

Quantitative, chemiluminescent immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Atellica IM Total hCG (ThCG)

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1155 Human chorionic gonadotropin test system

2. Classification:

   Class II

3. Product code:

   JHI

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indication for use below.

2. Indication(s) for use:

   The Atellica IM Total hCG (ThCG) assay is for in vitro diagnostic use in the quantitative determination of human gonadotropin (hCG) in human serum using the Atellica IM Analyzer.

   The Atellica IM ThCG assay is intended as an aid in the early detection of pregnancy.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   For use on the Atellica IM Analyzer

I. Device Description:

The Atellica IM Total β-hCG (ThCG) assay is a chemiluminescent immunoassay previously cleared for use on the Ciba-Corning ACS system in k925277. The Atellica IM System instrument was previously cleared as the Trinidad IM instrument under k151792; the new name of the system is the Atellica IM Analyzer.

The Atellica IM Total (ThCG) assay consists of the following reagents:

- Lite Reagent: 5.0 mL reagent pack contains goat polyclonal anti-hCG (~0.1 µg/mL) labeled with acridinium ester in buffered saline, sodium azide (0.1%), and preservatives.
- Solid Phase Reagent: 22.5 mL reagent pack monoclonal anti-hCG antibody (~0.02 mg/ml) covalently linked to paramagenetic particles, buffered saline, sodium azide (0.1%), and preservatives.
- Master Curve card: The master curve values are contained on a card that is provided with each kit.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ADVIA Centaur Total (ThCG) assay

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

   k925277

3. Comparison with predicate:

Similarities and Differences		
Item	Candidate Device Atellica IM Total (ThCG) Assay	Predicate Device ADVIA Centaur Total (ThCG) Assay k925277
Intended Use	For in vitro diagnostic use in the quantitative determination of human chorionic gonadotropin (hCG) in serum. This system is intended for use as an aid in the early detection of pregnancy.	Same
Detection Antibody	Goat polyclonal anti-hCG antibody labeled with acridinium ester	Same
Capture Antibody	Mouse monoclonal anti-hCG antibody coavalently coupled to paramagnetic particles	Same
Assay Principle	Chemiluminescence sandwich immunoassay	Same
Sample type	Serum	Same
Analytical measuring range	2.6-1000 mIU/mL (IU/L)	2.0-1000 mIU/mL (IU/L)
Analyzer	Atellica IM System	Ciba-Corning ACS System
Sample Volume	25 µL	50 µL
Reagent Volume	50 µL of Lite Reagent and 225 µL of Solid Phase	100 µL of Lite Reagent and 450 µL of Solid Phase
Incubation Time	8 minutes at 37°C	7.5 minutes at 37°C

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

CLSI EP5-A3 Evaluation of Precision Performance of Quantitative Measurement Methods, Approved Guideline-Third Edition

CLSI EP6-A Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach, Approved Guideline

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures, Approved Guideline–Second Edition

CLSI EP7-A2 Interference Testing in Clinical Chemistry, Approved Guideline –Second Edition

CLSI EP9-A3 Method Comparison and Bias Estimation Using Patient Samples, Approved Guideline – Third Edition

CLSI EP28-A3c Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, Approved Guideline – Third Edition

CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents, Approved Guideline

L. Test Principle:

The Atellica IM Total (ThCG) assay is a 2-site sandwich immunoassay using direct chemiluminescent technology that employs a goat polyclonal anti-hCG antibody labeled with acridinium ester and a purified mouse monoclonal anti-hCG secondary antibody, which is covalently bound to paramagnetic particles. These 2 antibodies are specific for different epitopes that are present on both the free ß-subunit and the ß-subunit of intact hCG.

A direct relationship exists between the amount of hCG 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 studies were conducted using two lots of Atellica IM Total (ThCG) reagent and two Atellica IM analyzers. Testing was performed two times a day with 2 replicates for 20 non-consecutive days for a total of 80 replicates. This study was performed using 3 spiked human serum samples and 3 human serum based control samples.
   Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of CLSI EP5-A2. In addition, an estimate of the repeatability, between-run, between-day, and within-laboratory precision using the restricted maximum likelihood method (REML) method was conducted. Precision results from all reagent lots and all systems (n=320) are shown below:

Sample	Mean	Repeatability		Between-run		Between-day		Within-lab	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum 1	2.4	0.21	8.8	0.08	3.3	0.11	4.7	0.25	10.5
Serum 2	12.6	0.36	2.8	0.2	1.6	0.12	1.0	0.43	3.4
Serum 3	782.0	14	1.8	6.89	0.9	6.73	0.9	17	2.2
Control 1	6.8	0.31	4.5	0.02	0.3	0.2	3.0	0.37	5.5
Control 2	23.4	0.6	2.6	0.39	1.7	0.37	1.6	0.81	3.5
Control 3	202.1	3.62	1.8	2.35	1.2	3.44	1.7	5.52	2.7

b. *Linearity/assay reportable range:*

Linearity

Linearity was established by preparing eleven sample dilutions at concentrations from 5.6 -1138 mIU/mL by mixing different proporitions of a normal human pregnant female hCG serum sample with a normal human serum sample without detectable hCG. The samples were tested with the Atellica IM Total (ThCG) assay on one analyzer in triplicate with two reagent lots. Results from the two reagent lots were similar. The expected values were plotted against the recovered hCG values. Linear regression gave the following equation:

$y = 1.037x + 1.619$, $R^2 = 0.9977$

The data support an analytical measuring range of 2.6-1000 mIU/mL.

Dilution Studies

A dilution recovery study was performed using 9 unique human serum samples (1200-14000 mIU/mL) to demonstrate the accuracy of dilution of samples above the reportable range of the candidate device. Dilutions for each sample were made with hCG negative serum pool (1/2, 1/4, 1/8, 1/16 dilutions) resulting in sample concentrations of approximately 185 – 900 mIU/mL.

This study was run on one instrument using one reagent pack lot. Each sample dilution was measured in triplicates. Percent recovery was calculated for each sample as shown below:

Sample Number	Dilution	Observed Mean (mIU/mL)	Expected Mean (mIU/mL)	% Recovery
1	Neat	-	1200.0	-
	1:2	543.0	600.0	91
2	Neat	-	1800.0	-
	1:2	822.0	900.0	91
	1:4	456.4	450.0	101
	1:8	232.9	225.0	104
	Mean			99
3	Neat	-	1600.0	-
	1:2	724.4	800.0	91
	1:4	412.1	400.0	103
	Mean			97
4	Neat	-	3000.0	-
	1:4	737.0	750.0	98
	1:8	403.7	375.0	108
	1:16	403.7	375.0	108
	Mean			105

Sample Number	Dilution	Observed Mean (mIU/mL)	Expected Mean (mIU/mL)	% Recovery
1	Neat	-	1200.0	-
	1:2	543.0	600.0	91
5	Neat	-	6000.0	0
	1:8	652.1	750.0	87
	1:16	351.9	375.0	94
	Mean			90
6	Neat	-	5000.0	-
	1:8	599.3	625.0	96
7	Neat	-	7000	-
	1:8	830.3	875.0	95
	1:16	464.3	437.5	106
	Mean			101
8	Neat	-	10000.0	-
	1:16	606.9	625.0	97
9	Neat	-	14000.0	-
	1:16	821.0	875.0	94

The recoveries ranged from 87% to 108% with mean recoveries of 91%, 101%, 98% and 100% for dilution factors 1/2, 1/4, 1/8, and 1/16. The Instructions for Use recommends diluting and retesting samples with hCG levels > 1000 mIU/mL to obtain accurate results.

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

The calibrators for the Atellica IM Total (ThCG) Assay are traceable to the World Health Organization (W.H.O.) 4th Internation Standard (IS) for hCG (75/589) and were cleared under k920372.

d. *Detection limit:*
The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantification (LoQ) were evaluated in accordance with CLSI EP17-A2 Guideline using the Atellica IM Total (ThCG) System.

Limit of blank:

The limit of blank was determined by testing five blank samples consisting of buffer based diluents and delipidized human serums. The samples were tested with 2 reagent lots on one instrument, once per day, 20 replicates per sample for 3 days yielding a total of 300 blank measurements per reagent lot. The limit of blank was determined non-parametricically. The highest value of the two reagent lots was the limit of blank. The limit of blank was determined to be 1.5 mIU/mL.

Limit of detection

Low-level hCG samples (1.7 mIU/mL and 2.9 mIU/mL) were prepared from five human serum pools spiked with patient samples with hCG. These samples were tested with 2 reagent lots on one instrument, once per day, 20 replicates per sample for 3 days yielding a total of 300 measurements per reagent lot. The LoD, 1.7 mIU/mL, was determined parametrically using the highest LoD from the two reagent lots.

Limit of quantitation:

Five low-level hCG samples were prepared from β-hCG negative human serum samples spiked with WHO β-hCG stock. These samples were tested with 2 reagent lots on one instrument in 5 replicates per run, 2 runs per day over 5 days (N=50 per sample per lot). The assay LoQ claimed by the sponsor from the worst lot is 2.6 mIU/mL based on a total error goal of bias and precision ≤ 30%.

e. *Analytical specificity:*

Cross-Reactivity:

To determine the cross-reactivity of related proteins in the Atellica IM Total (ThCG) assay, four human serum samples with hCG levels of approximately 2.2, 5, 50, and 500 mIU/mL, were spiked with Thyroid Stimulating Hormone (TSH), Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin (PRL), and Human Growth Hormone (hGH) and assayed using two reagent lots on one Atellica IM analyzer. Results from these cross-reactant spiked samples were evaluated against that of the serum without potential cross-reactants. No cross-reactivity (defined by the sponsor as < ±10% bias between the test pool and control pool for samples) was observed at the concentrations that were tested for PRL, hGH , TSH, LH, and FSH as shown below.

Substance	Concentration
TSH	1 mIU/mL
LH	500 mIU/mL
FSH	500 mIU/mL
PRL	1000 ng/mL
hGH	500 mg/mL

Interference Study:

Two human serum pools spiked with hCG to final concentrations of 5 mIU/mL and 500 mIU/mL were spiked with various endogenous substances and therapeutic drugs. All samples were tested in triplicate with two reagent lots on one Atellica IM system. Results from these spiked serum samples were compared to results of serum without potential interferenents. There was no significant interference (defined by the sponsor as < ±10% between the test pool and the control pool) up to the concentrations summarized below.

Potential interfering substances	Highest interferent concentration tested at which no significant interference was observed
Atropine	20 mg/dL
Bilirubin, conjugated	40 mg/dL
Bilirubin, unconjugated	40 mg/dL
Caffeine	308 µg/L or 0.0308 mg/dL
EDTA	3.4 µmol/L
Ethanol	100 mg/dL
Gentisic acid	117 µmol/L or 0.0117 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides (Intralipid)	3 g/L
Acetaminophen	20 mg/dL
Acetylsalicyclic acid	65 mg/dL
Heparin	7200 U/dL
Albumin	6 g/L
Ibuprofen	50 mg/dL

Hook effect:

Samples with hCG concentrations up to 1.0 million mIU/mL were prepared by spiking human hCG antigen to a pool of normal human serum, and were tested with the candidate Atellica IM Total (ThCG) assay. No hook effect was observed at hCG concentrations up to 1.0 million mIU/mL.

The sponsor includes the following statement in the labeling regarding hook effect:

"High ThCG concentrations can cause a paradoxical decrease in the RLUs (high-dose hook effect). In this assay, patient samples with hCG concentrations as high as 1,000,000 mIU/mL (IU/L) will report > 1000.0 mIU/mL (IU/L). Results were established using the Atellica IM Analyzer."

Human Anti-Mouse Antibodies:

To determine the susceptibility of the Atellica IM Total (ThCG) assay to potential human anti-mouse antibody (HAMA) interference, three patient samples and two control samples containing HAMA up to 1500 ng/mL were spiked with low and high hCG (6.5 mIU/mL and 501 mIU/mL). No HAMA interference at a concentration up to 1500 ng/mL was observed.

The sponsor includes the following statement in the Limitations section of the labeling:

"Identified sources of interference that have the potential to bind to and interfere with

any component of the assay include: heterophile and human anti-mouse antibodies (such as anti-mouse (HAMA), anti-rabbit, anti-goat)."

f. Assay cut-off:

Not applicable; this is a quantitative assay.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 107 unaltered and 8 altered serum samples were evaluated in singlet with the candidate Atellica IM Total (ThCG) System and the predicate ADVIA Centaur Total (ThCG) assay (k972525). The sample values ranged from 2.4 – 947.7 mIU/mL on the predicate device, and 2.3 – 897.8 mIU/mL on the candidate device. The results are summarized in the table below.

Parameter	Deming Regression
n	115
Slope	0.937
Intercept	0.234
R	0.999
Sample Range	2.4-947.7 mIU/mL

b. Matrix comparison:

Not applicable.

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:

Serum samples from 192 apparently healthy non-pregnant women ages 17-54 and 174 postmenopausal women aged ≥ 41 were tested in singlicate with the Atellica IM Total (ThCG) assay. The 2.5 and 97.5 percentiles of the concentration values were considered the expected value range of the Atellica IM Total (ThCG) assay. Results are listed below:

Reference Population age (years)	N subjects	Median (mIU/mL)	95% CL of Normal Range (mIU/mL)	95% CL of Lower Range (mIU/mL)	95% CL of Upper Range (mIU/mL)
17-54	192	2.0	1.5-4.2	1.4-1.6	3.5-4.8
≥ 41	174	3.9	1.8-10.1	1.5-1.9	8.1-13.8

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.