510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k091867

B. Purpose for Submission:

New device

C. Measurand:

Sex hormone-binding globulin (SHBG)

D. Type of Test:

Quantitative, chemiluminescent

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

ADVIA Centaur SHBG ReadyPack
SHBG Low Calibrator
SHBG High Calibrator
SHBG Master Curve Material

G. Regulatory Information:

Device Name	Product Code	Device Classification	Regulation Number	Panel
SHBG Calibrators	JIT	II	21 CFR 862.1150	Chemistry (75)
ADVIA Centaur SHBG ReadyPack	CDZ	Class I, reserved	21 CFR 862.1680	Chemistry (75)
SHBG Master Curve Material	JJX	Class I, reserved	21 CFR 862.1660	Chemistry (75)

H. Intended Use:

1. Intended use(s):

See Indications for Use below.

2. Indications(s) for use:

The ADVIA Centaur SHBG assay is an in vitro diagnostic immunoassay for the quantitative determination of sex hormone-binding globulin (SHBG) in human serum and plasma using the ADVIA Centaur systems. The ADVIA Centaur SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.

The ADVIA Centaur SHBG Calibrators are for in vitro diagnostic use in calibrating the ADVIA Centaur sex hormone-binding globulin (SHBG) assay.

The ADVIA Centaur SHBG Master Curve Material (MCM) is for in vitro diagnostic use in the verification of calibration and reportable range in the ADVIA Centaur sex hormone-binding globulin (SHBG) assay.

3. Special conditions for use statement(s):
For prescription use only

Not for newborn testing

SHBG Calibrators barcode labels are lot-number specific and should not be used with other calibrator lots.

SHBG Master Curve Material is not intended for use as routine quality control material or as calibration material.

4. Special instrument requirements:

ADVIA Centaur

I. Device Description:

Each SHBG Ready Pack contains: 1) Solid Phase (11.0 mL) streptavidin coupled magnetic latex particles (~150 μg/mL), 2) Lite Reagent (3.0 mL) containing mouse monoclonal anti-SHBG antibody (~130 μg/mL) labeled with acridinium ester, and 3) Ancillary Well Reagent (3.0 mL) containing a biotinylated monoclonal mouse anti-SHBG antibody (~6 μg/mL). Each Ready Pack contains reagents for 50 tests.

SHBG Calibrators are listed in the SHBG Ready Pack labeling as required by not provided. They contain 2 vials (2 mL/vial after reconstitution) each of lyophilized Low (~10 nmol/L) and High (~160 nmol/L) calibrators, a calibrator assigned value card, and lot specific barcode labels. Calibrators contain low or high levels of SHBG in equine serum, detergents and preservatives.

The ADVIA SHBG Master Curve Materials (MCM) are listed in the SHBG kit labeling as an optional reagent. It contains 5 levels of human SHBG in equine serum provided as 5 vials of lyophilized material (1 mL/ vial after reconstitution). MCM Levels 1-4 are expected to be in the acceptable range, while Level 5 is manufactured to meet or exceed the reportable range of the assay.

The product inserts for the SHBG Calibrators and SHBG Master Curve Material include the following statement: Human source material used in the manufacture of this product has been tested using FDA approved methods and found to be non-reactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis C (HCV), and antibody to HIV-1/2.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Elecsys SHBG Immunoassay System

   Roche Elecsys SHBG CalCheck

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

   k031717, k031698

3. Comparison with predicate:

Reagent Similarities and Differences		
	Device ADVIA Centaur SHBG assay	Predicate (Elecsys SHBG Immunoassay, k031717)
Intended Use	The ADVIA Centaur SHBG assay is an in vitro diagnostic immunoassay for the quantitative determination of sex hormone-binding globulin (SHBG) in human serum and plasma using the ADVIA Centaur Systems. The ADVIA Centaur SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.	Same
Assay Protocol	Sandwich Immunoassay	Same
Sample type	Serum and Lithium Heparin Plasma	Same
Test Methodology	Chemiluminescent Magnetic Latex Particle Immunoassay	Chemiluminescent solid phase enzyme Immunoassay

Reagent Similarities and Differences		
	Device ADVIA Centaur SHBG assay	Predicate (Elecsys SHBG Immunoassay, k031717)
Measuring Range	0.35 to 180 nmol/L	0.35 to 200 nmol/L

Calibrator Similarities and Differences		
	Device ADVIA SHBG Calibrators	Predicate (k031717)
Intended Use	The ADVIA Centaur SHBG Calibrators are for in vitro diagnostic use in calibrating the ADVIA Centaur sex hormone-binding globulin (SHBG) assays.	The Elecsys SHBG CalSet is used for calibrating the quantitative Elecsys SHBG assay on the Elecsys immunoassay systems.
Calibrator composition	Calibrator 1 contains approximately 10 nmol/L SHBG; Calibrator 2 contains approximately 160 nmol/L SHBG	Calibrator 1 contains approximately 0 nmol/L SHBG; Calibrator 2 contains approximately 40 nmol/L SHBG
Matrix	Equine serum	Calibrator 1 is in equine serum; Calibrator 2 is in human serum

Master Curve Material Similarities and Differences		
	Device ADVIA SHBG Master Curve Material	Predicate (k031698)
Intended Use	The ADVIA Centaur SHBG Master Curve Material are for in vitro diagnostic use in the verification of calibration and reportable range in the ADVIA Centaur sex hormone-binding globulin (SHBG) assay	The Elecsys SHBG CalCheck is intended for use in the verification of the calibration established by the Elecsys SHBG reagent
Levels	5 levels at approximately 0, 10, 50, 100, 200 nmol/L SHBG in equine serum	3 levels at approximately 20, 81 and 163 nmol/L SHBG in equine/human serum

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

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition (CLSI EP5-A2).
- Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (CLSI EP17-A).
- Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition (CLSI EP7-A2).
- Guidance for Industry and FDA Staff: Bundling Multiple Devices or Multiple Indications in a Single Submission

- Guidance for Industry – Abbreviated 510(k) Submissions for In Vitro Diagnostic Calibrators

L. Test Principle:

The ADVIA Centaur SHBG assay is a quantitative antibody sandwich immunoassay intended for use as an aid in the differential diagnosis of hirsutism and other adrenal abnormalities. The SHBG assay consists of streptavidin magnetic latex particles as the solid phase, biotin labeled anti-SHBG antibody as the capture conjugate, and an acridinium labeled anti-SHBG conjugate as the Lite reagent. An antibody sandwich is formed when SHBG in the patient sample or calibrator is captured by the anti-SHBG on the solid phase which then binds the anti-SHBG antibody acridinium ester (AE) conjugate.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The sponsor performed Within Run and Total precision studies according to the CLSI EP5-A2 guideline. Seven samples at various levels of SHBG were evaluated: five samples were pooled human serum samples at levels 9.04, 37.89, 72.84, 116.92 and 142.87 nmol/L, and two samples were human serum based control material at levels 21.42 and 39.87 nmol/L.

Five of the samples (1-5 below) were assayed 2 times, in 2 runs, on 1 ADVIA Centaur analyzer, (n = 80 for each sample), over a period of 20 days (n=80). Two additional serum samples (samples 6 and 7) were assayed 2 times, in 2 runs, on 1 ADVIA Centaur analyzer (n=40), over a period of 10 days. One trained operator performed the study.

			Within Run		**Total**	
Sample	**Mean (nmol/L)**	**N**	**SD**	**%CV**	**SD**	**%CV**
Level 1	9.04	80	0.28	3.1	1.59	6.5
Level 2	21.42	80	0.82	3.8	0.93	4.3
Level 3	37.39	80	1.12	3.0	1.96	5.2
Level 4	39.87	80	1.03	2.6	1.53	3.8
Level 5	72.84	80	2.61	3.6	4.20	5.8
Level 6	116.92	40	3.02	2.6	3.57	3.1
Level 7	142.87	40	3.57	2.5	5.49	3.8

b. Linearity/assay reportable range:

A linearity study was performed using a high pool and a low pool samples. Intermediate 10 levels were prepared from these two pool samples. A total of 12 samples ranging from 0.16 to 189.89 nmol/L which encompasses the claimed reportable range of 0.35 to 180 nmol/L were tested in triplicate. The measured values were plotted against the expected values and an appropriate line fitted by standard linear regression resulting in : y=1.011x+0.3897. The recovery results are presented below:

Sample	Dilution	Expected (nmol/L)	Measured (nmol/L)	Recovery (%)
1	High Sample	189.89	189.89	100.0
2	1:2	95.15	100.94	106.1
3	1:4	48.03	50.37	104.9
4	1:8	24.28	24.97	102.8
5	1:16	12.73	12.18	95.7
6	1:32	6.45	6.54	101.4
7	1:64	3.32	3.54	106.7
8	1:128	1.75	1.82	104.2
9	1:256	0.96	1.10	114.8
10	1:518	0.56	0.61	108.9
11	1:1036	0.36	0.38	106.5
12	Low Sample	0.16	0.16	100.0

In addition, the sponsor performed a dilution study to demonstrate the ability of the ADVIA Centaur analyzer to recovery accurately from a diluted sample using a 1:2 dilution. Thirteen human patient samples with high SHBG concentrations (140.3 to 306.8 nmol/L) near or above the assay upper limit of 180 nmol/L were diluted both manually and onboard the ADVIA Centaur analyzer and assayed using the ADVIA Centaur SHBG assay. One trained operator performed the study and the percent recovery calculated by comparing the observed onboard diluted results to the manually diluted results. The mean recovery results are within 98.86 and 118.72 %.

High-dose hook effect: The potential for a high-dose hook effect was evaluated for this assay. SHBG was spiked into negative pool (equine serum) and into 2 different serum samples to achieve SHBG concentrations ranging from 888 to 11,100 nmol/L. The samples were analyzed in triplicate on one ADVIA Centaur analyzer using 2 reagent lots. Based on the results, the sponsor concluded that SHBG levels < 1000 nmol/L did not exhibit any high dose effect.

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

Traceability:
The ADVIA Centaur SHBG assay is traceable to World Health Organization (WHO) standard (95/560). Assigned values of calibrators and ranges of controls are traceable to this standardization.

The ADVIA Centaur SHBG Calibrators, low and high: A set of internal SHBG standards were manufactured and value assigned using a SHBG WHO standard (NIBSC Code: 95/960). SHBG master lot calibrators are then value assigned against these standards by pooling the results using multiple ADVIA Centaur analyzers, multiple reagent lots and multiple runs. Productions lots are value assigned against Master lots by assaying replicate samples alternating between the "master lot" calibrator and the production lot (test lot) calibrator.

The SHBG Calibrator insert refers to the Calibrator Assigned Value card to facilitate entering the calibrator values on the system. Values for the Low (~10 nmol/L) and High (~160 nmol/L) calibrators are provided on the SHBG calibrator card.

The ADVIA SHBG Master Curve Material (MCM) is value assigned against an existing MCM reference lot that is traceable to a WHO SHBG standard (NIBSC Code: 95/960). Assigned values were established using the ADVIA Centaur SHBG assay and ADVIA Centaur analyzer. The target values for the 5 MCM solutions, MCM1 to MCM5 are 0, 10, 50, 100, and 200 nmol/L. Test lots are value assigned against the reference lot by assaying replicate samples alternating between the "reference lot" and the test lot. SHBG Master Curve Material product insert refers to the SHBG MCM lot specific target value sheet for the actual ranges.

Stability:

Real time shelf life and open vial stability testing protocols and acceptance criteria for the ADVIA Centaur SHBG Calibrators were reviewed and found to be acceptable. The product insert recommends storing the lyophilized calibrators at 2 to 8°C until expiration date on the vial label. The sponsor recommends a 39 week stability. It is recommended by the sponsor that the reconstituted calibrators be stored at -20°C for 60 days and to freeze-thaw once.

Real time shelf life stability protocols and acceptance criteria for the ADVIA SHBG Master Curve Material were reviewed and found to be acceptable. The sponsor recommends in the insert to store unopened MCM material at 2 to 8°C until the expiration date on the vial. The sponsor is recommends a 39 week stability. Once reconstituted the material should be used immediately and any remaining material discarded.

d. Detection limit:

The sponsor performed Limit of Blank (LoB) and the Limit of Detection (LoD) studies in accordance with the CLSI EP17-A guideline. For the LoB studies 5 negative SHBG base pools (horse serum) were used as blanks and were analyzed on two ADVIA Centaur analyzers over three days, with two replicates each, using two reagent lots. A total of 120 results were generated. A nonparametric analysis was employed and the LoB is reported as 0.0033 nmol/L.

For the LoD studies 5 spiked low SHBG pools with mean values ranging from 0.119 to 0.216 nmol/L were used. The pools were analyzed with 2 different reagent lots, on 2 ADVIA Centaur analyzers, over 3 days with 2 replicates/sample/run for a total of 24 replicates per sample. A total of 120 replicates were analyzed.

The mean, median and 5th percentiles were calculated for each sample by reagent lot by system. The LoD, the lowest level material in which the 5th percentile exceeds the Limit of Blank, was determined nonparametrically since the requirement of normality was not met for these pools for all combinations of reagent lot and system. The LoD was estimated to be 0.164 nmol/L.

The SHBG assay has a linearity range of 0.35 to 180 nmol/L.

c. Analytical specificity:

The sponsor performed interference studies according to the CLSI EP7-A guideline. Potential cross-reactive compounds (see table below) were added to steroid-free diluent and were evaluated in triplicate on ADVIA Centaur instrument using 2 reagent lots. Each test sample was compared to a matched unspiked control and the % change calculated. The sponsor defines no significant cross-reactivity as <5% difference from sample and control results and states that all the following tested cross reactants are within these specifications:

Potential Cross-Reactive Agent	**Spiking Concentration**
Alpha-Fetoprotein (AFP)	48.4 μg/dL
Cortisol	100 μg/mL
11-Deoxycortisol	4 μg/mL
5α-Dihydroxytestosterone	20 μg/mL
Estradiol	3600 pg/mL
Testosterone	20 μg/mL
Thyroglobulin	300 μg/mL
Thyroxin-Binding Globulin	193 μg/mL
Transferrin	4 mg/mL
Fibrinogen	4.5 g/L

Plasminogen	250 mg/L
IgA	367 mg/dL
IgG	335 mg/dL
CBG	35 mg/dL
TSH	180 mlU/L

Potential interfering substances were added to three sample pools containing 10, 50, and 80 nmol/L SHBG. The following interfering substances were added to these sample pools and assayed on an ADVIA Centaur in replicates of six: 5 mg/dL conjugated bilirubin and unconjugated bilirubin, 10, 30, 60 and 100 ng/dL biotin, 250 and 500 mg/dL of hemoglobin, 50 mg/mL of BSA, 50 ul/mL intralipid (equivalent to 1000 mg/dL triglyceride), and 1, 10, 100 ul/mL Silwet. The same samples pools containing the appropriate solvent of diluent used to dissolve the interferents were used as controls and the percent recovery between the samples and controls were calculated. The sponsor defines no significant interference as <10% change in results, and states that no significant interference was observed with any of the potential interferents tested. The labeling includes the following limitation: Samples that contain bilirubin concentrations greater than 5 mg/dL may be inaccurate due to potential interference and should not be used.

d. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparisons to the predicate device were performed in accordance with the CLSI EP9-A2 guideline.

A total of 202 remnant, de-identified serum samples, ranging from 0.37 to 172.72 nmol/L SHBG were tested in duplicate at one clinical site on the ADVIA Centaur analyzer (Y) and were compared to results of samples analyzed in duplicate on the Roche Elecsys 2010 (the predicate) (X). Data was analyzed using a singlet set of data from the candidate device. The analysis by least squares linear regression resulted in: $y = 0.94x + 2.7$; $r = 0.990$.

b. Matrix comparison:

The sponsor performed a matrix comparison study using a set of matched donor samples types (Serum, Lithium heparin plasma). Fifty nine samples, ranging from 15 to 142 nmol/L of SHBG, were analyzed. Nine of the donor samples were spiked with SHBG. Samples were measured in triplicate using one reagent lot and one ADVIA Centaur analyzer. The results of linear regression analysis: $y = 1.0331x - 0.0709$; $R^2 = 0.9924$.

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 of 69 healthy, non-pregnant, pre-menopausal women, 80 post-menopausal women, and 125 health males were used to establish reference ranges for SHBG. Samples were screened for the following and were included in the study only if concentrations fell within these ranges:

	Females Pre-menopausal	**Females Post-menopausal**	**Males**
TSH3UL adults (uIU/mL)	0.55-4.78	0.55-4.78	0.55-4.78
ThCG (non-pregnant) (mIU/L)	<5		
E2-6 III (pg/mL)	18.9-570.8	<50	
TSTO (ng/dL)	14-76	14-76	>175
FSH (uIU/mL)		23-116.3	
LH (uIU/mL)		15.9-54	

Samples were tested in duplicate using one lot of the ADVIA Centaur SHBG reagent, one ADVIA Centaur analyzer and one trained operator. Based on a central 95% interval, the following reference ranges were established:

	n	Age Range	SHBG Median (nmol/L)	5th Percentile (nmol/L)	95th Percentile (nmol/L)
Males	125	21-55	36.5	17.3	65.8
Females Pre-menopausal	69	21-47	61	27.8	146.5
Females Post-menopausal	80	42-89	62.6	12	166

The SHBG package insert states that each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.

Additionally, the sponsor performed a validation study using the ADVIA Centaur SHBG and the ADVIA Centaur Testosterone assays (k934562 originally the CIBA Corning Diagnostics Corp) and the same serum samples used to establish the SHBG reference ranges described above in section M5.

Samples were tested using single determinations with one lot of the ADVIA Centaur SHBG reagent and one lot of ADVIA Centaur testosterone reagent. The study was performed by one trained operator using on the ADVIA Centaur analyzer.

			Testosterone		
	n	Age	Median (ng/dL)	5th Percentile (ng/dL)	95th Percentile (ng/dL)
Males	125	21-55	487.1	231	735
Females Pre-menopausal	69	21-47	43	13.1	85.3
Females Post-menopausal	80	42-89	28.6	6	102.3

			FAI		
	n	Age	Median	5th Percentile	95th Percentile
Males	125	21-55	48	23.3	103.2
Females Pre-menopausal	69	21-47	2.7	0.64	9.4
Females Post- menopausal	80	42-89	1.86	0.3	9.6

The Free Androgen Index (%FAI) was obtained as follows: Testosterone (nmol/L)/SHBG (nmol/L) x 100.

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.