DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

June 29, 2016

SIEMENS HEALTHCARE DIAGNOSTICS INC.
MATTHEW GEE
SENIOR MANAGER, REGULATORY AFFAIRS
511 BENEDICT AVENUE
TARRYTOWN NY 10591-5097

Re: K151986
Trade/Device Name: ADVIA Centaur Testosterone II (TSTII),
ADVIA Centaur Testosterone II (TSTII) Master Curve Material,
ADVIA Centaur SHBG,
ADVIA Centaur SHBG Calibrator,
ADVIA Centaur SHBG Master Curve Material
Regulation Number: 21 CFR 862.1680
Regulation Name: Testosterone test system
Regulatory Class: I, reserved
Product Code: CDZ, JIT, JJX
Dated: June 3, 2016
Received: June 7, 2016

Dear Mr. Matthew Gee:

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,

Katherine Serrano -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)*
K151986

Device Name
ADVIA Centaur® Testosterone II (TSTII)
ADVIA Centaur® Testosterone II (TSTII) Master Curve Material

Indications for Use *(Describe)*
ADVIA Centaur® Testosterone II (TSTII)

The ADVIA Centaur Testosterone II (TSTII) assay is for in vitro diagnostic use in the quantitative determination of total testosterone (bound and unbound) in human serum and plasma using the ADVIA Centaur XP system.

Measurements of testosterone are used in the diagnosis and treatment of disorders involving the male sex hormones (androgens), including primary and secondary hypogonadism, delayed or precocious puberty, impotence in males and, in females, hirsutism (excessive hair) and virilization (masculinization) due to tumors, polycystic ovaries, and adrenogenital syndromes.

ADVIA Centaur® Testosterone II (TSTII) Master Curve Material

The ADVIA Centaur Testosterone II (TSTII) Master Curve Material is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur Testosterone II (TSTII) assay.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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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)*
K151986

Device Name
ADVIA Centaur® SHBG
ADVIA Centaur® SHBG Calibrator
ADVIA Centaur® SHBG Master Curve Material

Indications for Use *(Describe)*
ADVIA Centaur® SHBG

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 XP system.

The ADVIA Centaur SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.

ADVIA Centaur® SHBG Calibrator

For in vitro diagnostic use in calibrating the ADVIA Centaur SHBG assay on the ADVIA Centaur systems.

ADVIA Centaur® SHBG Master Curve Material

The ADVIA Centaur SHBG Master Curve Material is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur SHBG assay.

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: K151986

1. Date Prepared

June 27, 2016

2. Applicant Information

Contact: Matthew Gee, M.Sc.
Senior Manager, Regulatory Affairs

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3. Regulatory Information

Table 1. Regulatory Information for ADVIA Centaur TSTII Assay

Trade Name	ADVIA Centaur® Testosterone II (TSTII)
Model Numbers	10696862 (1-pack); 10696863 (5-pack)
Common Name	Radioimmunoassay, testosterones and dihydrotestosterone
Classification Name	Testosterone test system
FDA Classification	Class I (Reserved)
Review Panel	Clinical Chemistry (75)
Product Code	CDZ
Regulation Number	862.1680

Table 2. Regulatory Information for ADVIA Centaur TSTII Master Curve Material

Trade Name	ADVIA Centaur® Testosterone II (TSTII) Master Curve Material
Model Numbers	10492623
Common Name	Single (specified) analyte controls (assayed and unassayed)
Classification Name	Quality control material (assayed and unassayed)
FDA Classification	Class I
Review Panel	Clinical Chemistry (75)
Product Code	JJX
Regulation Number	862.1660

Table 3. Regulatory Information for ADVIA Centaur SHBG Assay

Trade Name	ADVIA Centaur® SHBG
Model Numbers	10997191 (1-pack)
Common Name	Radioimmunoassay, testosterones and dihydrotestosterone
Classification Name	Testosterone test system
FDA Classification	Class I (Reserved)
Review Panel	Clinical Chemistry (75)
Product Code	CDZ
Regulation Number	862.1680

Table 4. Regulatory Information for ADVIA Centaur SHBG Calibrator

Trade Name	ADVIA Centaur® SHBG Calibrator
Model Numbers	10997192
Common Name	Calibrator, Secondary
Classification Name	Calibrator
FDA Classification	Class II
Review Panel	Clinical Chemistry (75)
Product Code	JIT
Regulation Number	862.1150

Table 5. Regulatory Information for ADVIA Centaur SHBG Master Curve Material

Trade Name	ADVIA Centaur® SHBG Master Curve Material
Model Numbers	10997193
Common Name	Single (specified) analyte controls (assayed and unassayed)
Classification Name	Quality control material (assayed and unassayed)
FDA Classification	Class I
Review Panel	Clinical Chemistry (75)
Product Code	JJX
Regulation Number	862.1660

4. Predicate Device Information

ADVIA Centaur Testosterone II (TSTII)

Predicate Device Name: Elecys Testosterone II

510(k) Number: K093421

ADVIA Centaur Testosterone II (TSTII) Master Curve Material

Predicate Device Name: ADVIA Centaur Testosterone (TSTO) Master Curve Material

510(k) Number: K140505

ADVIA Centaur SHBG

Predicate Device Name: ADVIA Centaur SHBG

510(k) Number: K091867

ADVIA Centaur SHBG Calibrator

Predicate Device Name: ADVIA Centaur SHBG Calibrator

510(k) Number: K091867

ADVIA Centaur SHBG Master Curve Material

Predicate Device Name: ADVIA Centaur SHBG Master Curve Material

510(k) Number: K091867

5. Intended Use / Indications for Use

ADVIA Centaur Testosterone II (TSTII)

The ADVIA Centaur Testosterone II (TSTII) assay is for in vitro diagnostic use in the quantitative determination of total testosterone (bound and unbound) in human serum and plasma using the ADVIA Centaur XP system.

Measurements of testosterone are used in the diagnosis and treatment of disorders involving the male sex hormones (androgens), including primary and secondary hypogonadism, delayed or precocious puberty, impotence in males and, in females, hirsutism (excessive hair) and virilization (masculinization) due to tumors, polycystic ovaries, and adrenogenital syndromes.

ADVIA Centaur TSTII Master Curve Material

The ADVIA Centaur Testosterone II (TSTII) Master Curve Material is for *in vitro* diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur Testosterone II (TSTII) assay.

ADVIA Centaur SHBG

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 XP system.

The ADVIA Centaur SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.

ADVIA Centaur SHBG Calibrator

For *in vitro* diagnostic use in calibrating the ADVIA Centaur SHBG assay on the ADVIA Centaur systems.

ADVIA Centaur SHBG Master Curve Material

The ADVIA Centaur SHBG Master Curve Material is for *in vitro* diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur SHBG assay.

6. Device Description

Table 6. Summary of Ingredients of the ADVIA Centaur TSTII Assay Components

Component	Volume	Ingredients
ADVIA Centaur TSTII Primary Reagent ReadyPack (included in assay kit)		
ADVIA Centaur TSTII Lite Reagent	10.0 mL/pack	Acridinium ester-labeled hapten (36 µg/mL) in buffered saline with preservatives
ADVIA Centaur TSTII Solid Phase Reagent	17.0 mL/pack	Streptavidin-coated latex particles (0.33 g/L) in buffered saline with preservatives
ADVIA Centaur TSTII Ancillary Reagent ReadyPack (included in assay kit)		
ADVIA Centaur TSTII Releasing Agent	10.0 mL/pack	Steroid releasing agent (0.4 µg/mL) and biotinylated sheep monoclonal anti-testosterone antibody (27 µg/L) in buffered saline and preservatives
ADVIA Centaur TSTII Calibrator (included in assay kit)		
ADVIA Centaur TSTII Low and High Calibrators	2.0 mL/vial	After reconstitution, low or high levels of USP-grade estradiol, testosterone, cortisol, and progesterone spiked in charcoal-stripped, defibrinated human plasma with sodium azide (0.1%) and preservatives
ADVIA Centaur TSTII Master Curve Material (sold separately)		
ADVIA Centaur TSTII MCM1	1.0 mL/vial	Lyophilized human plasma with sodium azide (0.1% after reconstitution) and preservatives
ADVIA Centaur TSTII MCM2-7	1.0 mL/vial	Various levels of testosterone in lyophilized human plasma with sodium azide (0.1% after reconstitution) and preservatives

Table 7. Summary of Ingredients of the ADVIA Centaur SHBG Assay Components

Component	Volume	Ingredients
ADVIA Centaur SHBG Primary Reagent ReadyPack (included in assay kit)		
ADVIA Centaur SHBG Lite Reagent	3.0 mL/pack	Mouse monoclonal anti-SHBG antibody (~130 ng/mL) labeled with acridinium ester in HEPES-buffered saline with bovine serum albumin, mouse serum, sodium azide (< 0.1%), surfactant, and preservatives
ADVIA Centaur SHBG Solid Phase Reagent	11.0 mL/pack	Streptavidin coupled to latex paramagnetic particles (~150 µg/mL) in HEPES buffered saline with bovine serum albumin, mouse serum, sodium azide (< 0.1%), surfactant, and preservatives
ADVIA Centaur SHBG Ancillary Well Reagent	3.0 mL/pack	Biotinylated monoclonal mouse anti-SHBG antibody (~6 µg/mL) in HEPES buffered saline with bovine serum albumin, mouse serum, sodium azide (< 0.1%), surfactant, and preservatives
ADVIA Centaur SHBG Calibrator (sold separately)		
ADVIA Centaur SHBG Low and High Calibrators	2.0 mL/vial	After reconstitution, low or high levels of SHBG in equine serum, detergents and preservatives

Table 7. Summary of Ingredients of the ADVIA Centaur SHBG Assay Components

Component	Volume	Ingredients
ADVIA Centaur SHBG Master Curve Material (sold separately)		
ADVIA Centaur SHBG MCM1-5	1.0 mL/vial	Various levels of SHBG in equine serum with detergents and preservatives

7. Purpose of the Submission

The purpose of this submission is to submit a new device (ADVIA Centaur TSTII assay) and to submit a modification to the ADVIA Centaur SHBG assay due to the re-standardization to the WHO 2nd International Standard for SHBG (08/266).

8. Comparison of Predicate Device and Modified Device

Table 8. Comparison of ADVIA Centaur TSTII Assay to Predicate

Item	ADVIA Centaur Testosterone II (TSTII) Assay (Candidate Device)	Elecsys Testosterone II Assay (Predicate Device)
Intended Use	For *in vitro* diagnostic use in the quantitative determination of total testosterone (bound and unbound) in serum using the ADVIA Centaur and ADVIA Centaur XP Systems.	Immunoassay for the in vitro quantitative determination of testosterone in human serum and plasma. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.
Indications for Use	Measurements of testosterone are used in the diagnosis and treatment of disorders involving the male sex hormones (androgens), including primary and secondary hypogonadism, delayed or precocious puberty, impotence in males and, in females hirsutism (excessive hair) and virilization (masculinization) due to tumors, polycystic ovaries, and adrenogenital syndromes.	Same
Methodology	Chemiluminescence	Electrochemiluminescence
Assay Protocol	Competitive immunoassay	Same
Traceability/ Standardization	ID-LC-MS/MS (CDC HoSt Testosterone Reference Measurement Procedure)	ID-GC/MS
Specimen Type	Human serum and plasma	Same
Sample Volume	20 µL	Same
Lower Limit of Measuring Range	LoQ	LoD
Measuring Range	7.0–1500 ng/dL	2.5–1500 ng/dL
Calibration	2-point calibration	Same

Table 9. Comparison of ADVIA Centaur TSTII Master Curve Material to Predicate

Item	ADVIA Centaur Testosterone II (TSTII) MCM (Candidate Device)	ADVIA Centaur Testosterone (TSTO) MCM (Predicate Device)
Intended Use	The ADVIA Centaur Testosterone II (TSTII) Master Curve Material is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur Testosterone II (TSTII) assay.	The ADVIA Centaur Testosterone (TSTO) Master Curve Material is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur Testosterone assay.
Approximate Target Values (Actual Number Varies by Lot)	Level 1: 0.00 ng/dL Level 2: 50.0 ng/dL Level 3: 100.0 ng/dL Level 4: 500.0 ng/dL Level 5: 750.0 ng/dL Level 6: 1000.0 ng/dL Level 7: 1600.0 ng/dL	Same
Matrix	Lyophilized human plasma	Same
Value Assignment Process	Full curve testing	Two point nested testing

Table 10. Comparison of ADVIA Centaur SHBG Assay to Predicate

Item	ADVIA Centaur SHBG Assay: WHO 08/266 2nd IS (Candidate Device)	ADVIA Centaur SHBG Assay: WHO 95/560 1st IS (Predicate Device)
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 XP system.	Same
Indications for Use	The ADVIA Centaur SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.	Same
Methodology	Chemiluminescence	Same
Assay Protocol	Sandwich immunoassay	Same
Traceability/ Standardization	Standardized to WHO 2nd International Standard (08/266)	Traceable to WHO 1st International Standard (95/560)
Specimen Type	Human serum and plasma	Same
Sample Volume	10 µL	Same
Measuring Range	1.60–180 nmol/L	Same
Calibration	2-point calibration	Same

Table 11. Comparison of ADVIA Centaur SHBG Calibrator to Predicate

Item	ADVIA Centaur SHBG Calibrator: WHO 08/266 2nd IS (Candidate Device)	ADVIA Centaur SHBG Calibrator: WHO 95/560 1st IS (Predicate Device)
Intended Use	For in vitro diagnostic use in calibrating the ADVIA Centaur SHBG assay on the ADVIA Centaur systems.	Same
Target Values	Low Calibrator: 10.0 nmol/L High Calibrator: 140.0 nmol/L	Same
Matrix	Equine serum	Same
Traceability	WHO 2nd International Standard	WHO 1st International Standard
Value Assignment Process	Full curve testing	Two point nested testing

Table 12. Comparison of ADVIA Centaur SHBG Master Curve Material to Predicate

Item	ADVIA Centaur SHBG MCM: WHO 08/266 2nd IS (Candidate Device)	ADVIA Centaur SHBG MCM: WHO 95/560 1st IS (Predicate Device)
Intended Use	The ADVIA Centaur SHBG Master Curve Material is for in vitro diagnostic use in the verification of calibration and reportable range of the ADVIA Centaur SHBG assay.	Same
Approximate Target Values (Actual Number Varies by Lot)	Level 1: 0.1 nmol/L Level 2: 10.0 nmol/L Level 3: 50.0 nmol/L Level 4: 100.0 nmol/L Level 5: 200.0 nmol/L	Same
Matrix	Equine serum	Same
Traceability	WHO 2nd International Standard	WHO 1st International Standard
Value Assignment Process	Two point nested testing	Same

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 Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition (CLSI EP05-A2, 2004; Recognition No. 7-110)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP06-A, 2003; Recognition No. 7-193)
- Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition (CLSI EP07-A2, 2005; Recognition No. 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 No. 7-233)

- Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition (CLSI EP28-A3c – formerly C28-A3c, 2010; Recognition No. 7-224)
- Medical devices – Application of risk management to medical devices (ANSI/AAMI/ISO 14971:2007/(R)2010; Recognition No. 5-70)

10. Performance Characteristics: ADVIA Centaur TSTII

10.1 Precision

A 20-day precision study was performed according to CLSI EP5-A2. Samples included 5 serum patient pools, three levels of controls and one female patient serum specimen. Samples were assayed twice a day in replicates of 2, for 20 days (n = 80 replicates per sample). The following results were obtained:

Sample	Mean (ng/mL)	Repeatability		Within-Lab	
		SD (ng/mL)	%CV	SD (ng/mL)	%CV
Female Patient Serum Specimen	10.58	0.90	8.5	1.33	12.6
Serum Patient Pool 1	26.45	1.41	5.3	2.07	7.8
Serum Patient Pool 2	81.78	2.49	3.0	4.29	5.3
Serum Patient Pool 3	311.97	12.37	4.0	16.54	5.3
Serum Patient Pool 4	768.74	23.81	3.1	41.71	5.4
Serum Patient Pool 5	1127.07	54.15	4.9	77.67	6.9
Control 1	226.34	7.11	3.1	10.19	4.5
Control 2	578.19	19.28	3.3	34.53	6.0
Control 3	735.72	24.61	3.3	44.43	6.0

10.2 Linearity

A linearity study was performed using the modified device according to CLSI EP06-A using 11 serially diluted samples spanning the assay range. The mean was taken from each sample tested in duplicate. As presented below, the bias from the linear fit estimate was <10%.

Sample	Expected Dose (ng/dL)	Observed Dose (ng/dL)	Weighted Linear Fit Estimate	Deviation from Linear Fit (ng/dL)	Deviation from Linear Fit (%)
A	1653.77	1653.77	1521.25	132.52	8.71
B	1242.01	1155.85	1142.43	13.43	1.18
C	830.24	834.69	763.61	71.09	9.31
D	418.48	402.81	384.78	18.03	4.68
E	212.60	198.74	195.37	3.36	1.72
F	109.66	103.94	100.67	3.27	3.25
G	58.19	49.48	53.32	-3.84	-7.19
H	32.46	27.04	29.64	-2.59	-8.75
I	19.59	15.80	17.80	-2.00	-11.25
J	13.15	10.53	11.88	-1.35	-11.35
K	6.72	6.72	5.96	0.76	12.71

The weighted linear regression equation is presented below.

Observed = 0.92(Expected) - 0.22 ng/dL

10.3 Dilution Recovery

Five serum samples in the range of 1520.24–1715.58 ng/dL of testosterone were diluted 1:2 with ADVIA Centaur Multi-Diluent 3, and assayed for recovery. The recoveries ranged from 93.9 to 114.2% with a mean of 106.7%.

Sample	Dilution Factor	Observed Dose (ng/dL)	Expected Dose (ng/dL)	% Recovery
1	Neat	1581.78	1684.06	93.9%
	1:2	790.89	842.03	
2	Neat	1757.54	1636.03	107.4%
	1:2	878.77	818.01	
3	Neat	1730.52	1520.25	113.8%
	1:2	865.26	760.12	
4	Neat	1825.77	1598.79	114.2%
	1:2	912.89	799.39	
5	Neat	1782.64	1715.58	103.9%
	1:2	891.32	857.79	
Mean				**106.7%**

10.4 Method Comparison

A method comparison study was performed by comparing the ADVIA Centaur TSTII assay to the CDC HoSt Testosterone ID-LC-MS/MS method with 128 serum samples distributed over the assay range (8.61 to 1394.00 ng/dL). The analysis was performed using Passing-Bablok regression. The regression equation from the analysis is presented below.

ADVIA Centaur TSTII = 0.97(ID-LC-MS/MS) + 1.94 ng/dL (r = 0.98)

An additional method comparison study was performed against the Dimension Vista Total Testosterone assay (k151529) with 117 serum samples (56 samples from adults and 61 samples from pediatrics) ranging from 8.00 ng/dL to 825.00 ng/dL. An analysis was also performed with the 61 samples from pediatric subjects (27 females age 7 to 18 and 34 males age 9 to 18) ranging from 8.00 to 732.00 ng/dL. The analyses were performed using Weighted Deming regression. The regression equations from the analyses are presented below.

Adult and pediatric specimens:

ADVIA Centaur TSTII = 1.01(Dimension Vista TST) + 0.99 ng/dL (r = 0.99)

Pediatric specimens:

ADVIA Centaur TSTII = 1.04(Dimension Vista TST) + 0.22 ng/dL (r = 0.99)

10.5 Matrix Comparison

The ADVIA Centaur TSTII assay was evaluated using different specimen matrices and tube collection types. A specimen collection study was performed using a minimum of 50 matched specimens drawn in different tube types including serum red top, serum separator tube, plasma separator tube, dipotassium EDTA, lithium heparin, and sodium heparin. No significant difference between tube types was observed. The following results were obtained:

Tube Types	Slope	Intercept (ng/dL)	r
Serum vs. serum separator tube	0.98	3.76	0.991
Serum vs. plasma separator tube	0.94	3.56	0.993
Serum vs. dipotassium EDTA	0.97	-1.61	0.994
Serum vs. lithium heparin	0.95	4.50	0.996
Serum vs. sodium heparin	0.94	2.85	0.996

10.6 Reference Intervals

Reference intervals for the ADVIA Centaur TSTII assay were established for pediatrics and adults according to CLSI EP28-A3c.

Reference intervals for the ADVIA Centaur SHBG assay for adults according to CLSI EP28-A3c.

The adult population included samples from apparently healthy normal cycling women, postmenopausal women, and normal males. Based on a central 95% interval, the following reference intervals were established.

Testosterone

Group	n	Median (ng/dL)	Reference Values (ng/dL)
Males Age <50 (21-49)	119	388.24	123.06 – 813.86
Males Age ≥50 (50-89)	137	374.72	86.98 – 780.10
Females Pre-Menopause (Age 21-60)	167	22.26	9.01 – 47.94
Females Post-Menopause (Age 45-89)	127	15.18	< 7.00 – 45.62

SHBG

Group	n	Median (nmol/L)	Reference Values (nmol/L)
Males Age <50 (21-49)	122	34.97	14.55 –94.64
Males Age ≥50 (50-89)	137	52.49	21.63 –113.13
Females Pre-Menopause (Age 21-60)	167	58.21	10.84 – >180.00
Females Post-Menopause (Age 45-89)	134	61.44	23.15 – 159.07

FAI

Group	n	Median	Reference Values
Males Age <50 (21-49)	119	39.14	11.14 – 81.01
Males Age ≥50 (50-89)	137	27.17	8.99 – 46.51
Females Pre-Menopause (Age 21-60)	167	1.28	0.27 – 7.64
Females Post-Menopause (Age 45-89)	127	0.87	0.17 – 4.15

Reference intervals characterized by age and Tanner stage were established for the ADVIA Centaur TSTII assay for a pediatric population in accordance with the CLSI guideline EP28-A3c.

For groups of 120 or more subjects, the lower and upper reference limits were estimated as the 2.5th and the 97.5th percentiles of the distribution of test results using a non-parametric approach in accordance with the recommendation in CLSI guideline EP28-A3.

For groups of 40 to 119 subjects, the lower and upper reference limits were estimated as the 2.5th and the 97.5th percentiles of the distribution of test results using a robust measure of location and spread, as developed by Horn and Pesce.

For groups of less than 40 subjects, the lower and upper reference limits were estimated as the 5th and the 95th percentiles of the distribution of test results.

Samples were collected prospectively from apparently healthy pediatric subjects (good endocrinological health) using predefined inclusion criteria.

Group	n	Median (ng/dL)	Reference Values (ng/dL)
Males Age 2-10	40	< 7.00	< 7.00 – 29.44
Males Age 11	20	11.89	< 7.00 – 353.00
Males Age 12	25	70.30	< 7.00 – 562.42
Males Age 13	21	120.37	8.12 – 582.87
Males Age 14	31	284.90	20.35 – 777.38
Males Age 15	22	334.86	127.21 – 849.36
Males Age 16-21	44	456.26	113.19 – 882.10
Males Tanner Stage 1	36	< 7.00	< 7.00 – 47.43
Males Tanner Stage 2	38	11.79	< 7.00 – 174.45
Males Tanner Stage 3	44	250.44	10.54 – 802.75
Males Tanner Stage 4	44	356.12	63.89 – 736.20
Males Tanner Stage 5	42	458.24	55.69 – 897.40
Females Age 2-10	40	< 7.00	< 7.00 – 117.76
Females Age 11-15	130	16.03	< 7.00 – 38.92
Females Age 16-21	36	25.20	15.06 – 42.41
Females Tanner Stage 1	44	< 7.00	< 7.00 – 89.56
Females Tanner Stage 2	42	12.81	< 7.00 – 38.29
Females Tanner Stage 3	42	16.71	< 7.00 – 33.86
Females Tanner Stage 4	40	19.82	< 7.00 – 38.72
Females Tanner Stage 5	42	22.79	10.83 – 50.08

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 ADVIA Centaur TSTII assay has an LoB of 2.50 ng/dL, an LoD of 5.00 ng/dL, and an LoQ of 7.00 ng/dL.

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 testosterone that can be detected with 95% probability. The LoQ is defined as the lowest concentration of testosterone that can be detected at a total CV of 20%.

10.8 Interference

Interference studies were performed according to CLSI EP07-A2. Two sample pools were tested. One sample pool had approximately 30 ng/dL testosterone. The second sample pool had approximately 300 ng/dL testosterone. These sample pools were spiked with potential interferents. Control samples were prepared by spiking sample pools with the appropriate diluent at the same volume as the interfering substance stock. For substances spiked at doses that caused >10% interference, serial measurements were taken and analyzed by linear regression. Results are presented below.

Interferent	~30 ng/dL Testosterone			~300 ng/dL Testosterone		
	Dose Without Interferent (ng/dL)	Dose With Interferent (ng/dL)	% Interference	Dose Without Interferent (ng/dL)	Dose With Interferent (ng/dL)	% Interference
Hemoglobin (500 mg/dL)	32.16	34.02	5.8	240.66	239.81	-0.4
Triglycerides (1000 mg/dL)	31.23	31.61	1.2	233.78	213.84	-8.5
Conjugated Bilirubin (15 mg/dL)	20.21	21.05	4.2	269.61	258.61	-4.1
Unconjugated Bilirubin (20 mg/dL)	20.81	22.81	9.6	258.77	261.97	3.2
Cholesterol (500 mg/dL)	21.91	23.32	6.4	263.43	238.58	-9.4
Rheumatoid Factor (200 IU/mL)	24.46	25.59	4.6	271.95	273.98	0.7

The concentration of biotin that causes 10% interference, as determined by linear regression, is 30 ng/mL. Specimens that contain 40 ng/mL of biotin demonstrate a 14.6% change in results.

Samples with conjugated bilirubin concentrations > 15 mg/dL will cause erroneous results. Specimens that contain 20 mg/dL of conjugated bilirubin demonstrate a -14.4% change in results.

Samples with unconjugated bilirubin concentrations > 20 mg/dL will cause erroneous results. Specimens that contain 30 mg/dL of unconjugated bilirubin demonstrate a 20.1% change in results.

10.9 Heterophile Interference

Heterophile interference testing was performed by spiking 19 HAMA-positive serum samples with ~30 and ~300 ng/dL USP testosterone. The Expected Dose was calculated by adding the “spiked” testosterone concentration to the endogenous (neat) testosterone concentration of the sample. The percent recoveries were determined by dividing the Observed Dose by the Expected Dose. The mean recovery for all samples spiked with ~30 ng/dL USP testosterone was 98.69%. The mean recovery for all samples spiked with ~300 ng/dL USP testosterone was 94.55%.

10.10 Cross-Reactivity

Cross-reactivity studies were performed using two sample pools of approximately 0 ng/dL and 300 ng/dL testosterone. These sample pools were spiked with potential cross-reactants.

Control samples were prepared by spiking sample pools with the appropriate diluent at the same volume as the interfering substance stock. Results are presented below.

Potential Cross-Reacting Substance	~0 ng/dL Testosterone			~300 ng/dL Testosterone		
	Dose Without Substance (ng/dL)	Dose With Substance (ng/dL)	% Cross-Reactivity	Dose Without Substance (ng/dL)	Dose With Substance (ng/dL)	% Cross-Reactivity
5-Androstene-3β, 17β-diol (10,0000)	0.00	124.12	0.124	315.34	147.87	-0.167
Androstenedione (10,000)	1.98	141.69	1.397	329.36	240.73	-0.886
Androsterone (100,000)	2.18	4.99	0.003	320.65	294.93	-0.026
Canrenone (18,000)	2.18	2.25	0.000	320.65	332.50	0.066
Canrenone (50,000)	2.18	2.82	0.001	320.65	323.09	0.005
Canrenone (100,000)	2.18	2.70	0.001	320.65	329.04	0.008
Corticosterone (100,000)	2.18	1.72	0.000	320.65	334.39	0.014
Cortisol (100,000)	2.18	2.68	0.000	320.65	342.27	0.022
Cyproterone (10,000)	2.18	15.01	0.128	320.65	326.09	0.054
Danazol (100,000)	2.18	122.24	0.120	320.65	199.51	-0.121
11-Deoxycortisol (100,000)	2.18	4.11	0.002	320.65	322.85	0.002
Dexamethasone (100,000)	2.18	2.00	0.000	320.65	326.69	0.006
DHEA (100,000)	2.18	7.86	0.006	320.65	278.20	-0.042
DHEAs (5,000,000)	2.18	73.88	0.001	320.65	278.70	-0.001
5α-Dihydrotestosterone (10,000)	2.18	77.56	0.754	320.65	179.68	-1.410
17β-Estradiol (100,000)	0.09	21.12	0.021	355.52	88.27	-0.267
Estrone (10,000)	2.18	2.41	0.002	320.65	319.76	-0.009
Ethisterone (100,000)	0.00	445.99	0.446	271.00	678.95	0.408
11β-Hydroxytestosterone (10,000)	0.00	1546.85	15.469	271.00	1612.34	13.413
11-Keto-testosterone (100,000)	0.00	1765.93	1.766	271.00	1854.41	1.583
Nandrolone decanoate (100,000)	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*
Norgestrel (100,000)	0.00	145.01	0.145	271.00	197.62	-0.073

Potential Cross-Reacting Substance	~0 ng/dL Testosterone			~300 ng/dL Testosterone		
	Dose Without Substance (ng/dL)	Dose With Substance (ng/dL)	% Cross-Reactivity	Dose Without Substance (ng/dL)	Dose With Substance (ng/dL)	% Cross-Reactivity
Oxymetholone (10,000)	2.18	2.94	0.008	320.65	263.08	-0.576
Prednisolone (100,000)	0.00	0.00	0.000	271.00	364.17	0.093
Prednisone (100,000)	0.00	0.00	0.000	271.00	282.17	0.011
Progesterone (100,000)	2.18	2.45	0.000	320.65	335.04	0.014
Spironolactone (8,000)	2.18	2.59	0.005	320.65	329.06	0.105
Spironolactone (100,000)	2.18	2.09	0.000	320.65	331.68	0.011
Testosterone propionate (10,000)	0.00	3.54	0.035	271.00	565.56	2.946
7α-Thiomethyl spironolactone (40,000)	2.18	2.45	0.001	320.65	320.96	0.001
7α-Thiomethyl spironolactone (100,000)	2.18	2.40	0.000	320.65	318.27	-0.002

* Crossreactivity for this compound could not be calculated. This compound tested above the measuring interval.

10.11 Traceability and Value Assignment

The ADVIA Centaur TSTII assay is standardized using internal standards made from USP-grade testosterone, which are traceable to isotope dilution-liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS). The ID-LC-MS/MS is traceable to the primary testosterone standard National Measurement Institute (NMI) M914.

The calibrator values used for two-point calibration of the ADVIA Centaur TSTII assay are value assigned using standards traceable to the ID-LC-MS/MS method.

The ADVIA Centaur TSTII Master Curve Material assigned values are lot specific of target values.

10.12 Stability

The ADVIA Centaur TSTII Reagents, Calibrators and Master Curve Materials are stable until the date printed on the box label when stored at 2-8°C.

The onboard stability of the ADVIA Centaur TSTII Reagents is 18 days with a calibration interval of 28 days.

11. Performance Characteristics: ADVIA Centaur SHBG

11.1 Precision

A 5-day precision study was performed using the modified device to verify existing claims. Samples included 3 patient serum specimens, 2 patient pools and three levels of controls. Samples were assayed once a day in replicates of 5, for 5 days (n = 25 replicates per sample). The following results were obtained:

Sample	Mean (nmol/L)	Repeatability		Within-Lab	
		SD (nmol/L)	%CV	SD (nmol/L)	%CV
Patient specimen 1	70.71	1.58	2.2	1.89	2.7
Patient specimen 2	115.95	3.05	2.6	3.84	3.3
Patient specimen 3	145.59	4.39	3.0	6.44	4.4
Patient pool 1	10.69	0.21	1.9	0.26	2.4
Patient pool 2	39.89	0.72	1.8	0.82	2.1
Control 1	22.49	0.40	1.8	0.43	1.9
Control 2	44.95	0.96	2.1	0.99	2.2
Control 3	39.54	0.93	2.3	1.00	2.5

11.2 Linearity

A linearity study was performed using the modified device according to CLSI EP06-A using 11 serially diluted samples spanning the assay range. The mean was taken from each sample tested in duplicate. As presented below, the bias from the linear fit estimate was ≤15%.

Sample	Expected Dose (nmol/L)	Observed Dose (nmol/L)	Weighted Linear Fit Estimate	Deviation from Linear Fit (nmol/L)	Deviation from Linear Fit (%)
A	198.79	195.95	195.83	0.12	0.06
B	183.50	183.50	180.79	2.71	1.50
C	159.03	161.07	156.72	4.36	2.78
D	119.27	117.44	117.60	-0.16	-0.13
E	59.64	59.43	58.92	0.51	0.87
F	29.82	29.28	29.58	-0.31	-1.04
G	14.91	14.77	14.91	-0.15	-0.99
H	7.45	7.51	7.58	-0.07	-0.97
I	3.73	3.92	3.91	0.01	0.30
J	1.86	2.04	2.08	-0.04	-2.03
K	0.93	1.16	1.16	0.00	-0.10

The weighted linear regression equation is presented below.

Observed = 0.984(Expected) + 0.245 ng/dL

11.3 Dilution Recovery

Five serum samples in the range of 161.14-175.13 nmol/L of SHBG were diluted 1:2 with ADVIA Centaur Multi-Diluent 1, and assayed for recovery. The recoveries ranged from 87 to 101% with a mean of 92%.

Sample	Onboard Dilution Dose (nmol/L)	Manual Dilution Dose (nmol/L)	% Recovery
1	175.13	173.59	101%
2	164.64	188.37	87%
3	161.14	172.77	93%
4	162.89	181.78	90%
5	164.34	179.9	91%
Mean			**92%**

11.4 Method Comparison

A method comparison study was performed by comparing the ADVIA Centaur SHBG assay to the Elecsys SHBG assay with 174 serum samples distributed over the assay range. The analysis was performed using Weighted Deming regression. The regression equation from the analysis is presented below.

ADVIA Centaur SHBG = 0.99(Elecsys) - 0.11 nmol/L (r = 0.99)

11.5 Matrix Comparison

The re-standardization of the ADVIA Centaur SHBG assay did not influence sample matrices.

11.6 Reference Intervals

See Section 10.6 (Reference Intervals) for ADVIA Centaur TSTII assay.

11.7 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 ADVIA Centaur SHBG assay has an LoB of 1.2 nmol/L, an LoD of 1.6 nmol/L, and an LoQ of 1.8 nmol/L.

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 SHBG that can be detected with 95% probability. The LoQ is defined as the lowest concentration of SHBG that can be detected at a total CV of 20%.

11.8 Interference

The re-standardization of the ADVIA Centaur SHBG assay did not influence interference. This information is described in K091867.

11.9 Cross-Reactivity

The re-standardization of the ADVIA Centaur SHBG assay did not influence cross-reactivity. This information is described in K091867.

11.10 Traceability and Value Assignment

The ADVIA Centaur SHBG assay is standardized to World Health Organization (WHO) 2nd International Standard for SHBG, NIBSC code 08/266.

The calibrator values used for two-point calibration of the ADVIA Centaur SHBG assay are value assigned using standards prepared from SHBG standardized against gravimetrically prepared dilutions of the 2nd International Reference Preparation (WHO 08/266) from NIBSC.

The ADVIA Centaur SHBG Master Curve Material assigned values are lot specific of target values.

11.11 Stability

The re-standardization of the ADVIA Centaur SHBG assay did not influence stability. This information is described in K091867.

12. Conclusions

The new ADVIA Centaur Testosterone II (TSTII) assay (Reagents and Calibrators) is substantially equivalent in principle and performance to the currently-marketed predicate device, the Elecsys Testosterone II assay, cleared under 510(k) K093421.

The ADVIA Centaur TSTII Master Curve Material is substantially equivalent in principle and performance to the currently-marketed predicate device, the ADVIA Centaur Testosterone (TSTO) Master Curve Material, cleared under 510(k) K140505.

The modified ADVIA Centaur SHBG assay (Reagents, Calibrators, Master Curve Material) is substantially equivalent in principle and performance to the currently-marketed predicate device, the ADVIA Centaur SHBG assay, cleared under 510(k) K091867.