

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

A. 510(k) Number:

k133491

B. Purpose for Submission:

Modified polyclonal antibody

C. Measurand:

Testosterone

D. Type of Test:

Quantitative Chemiluminescent Immunoassay

E. Applicant:

Siemens Healthcare, Inc.

F. Proprietary and Established Names:

ADVIA Centaur Testosterone (TSTO)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CDZ	Class I, reserved	21 CFR 862.1680 Testosterone Test System	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indications for use below

2. Indication(s) for 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. 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.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

For use on the Siemens ADVIA Centaur and ADVIA Centaur XP systems.

I. Device Description:

The device consists of the following reagents:

1. Lite Reagent 2.5 mL/ reagent pack - The Lite Reagent contains acridinium ester-labeled testosterone (~3.2 ng/mL) in buffered saline with preservatives
2. Solid Phase 15.0 mL/ reagent pack - The Solid Phase reagent contains polyclonal rabbit anti-testosterone antibody (~0.06 µg/mL) bound to monoclonal mouse anti-rabbit antibody (~0.53 µg/mL) covalently coupled to paramagnetic particles in buffered saline with sodium azide (0.1%) and preservatives.
3. Probe Wash 10.0 mL/ reagent pack - The Probe Wash Reagent contains buffered saline with sodium azide (0.1%) and preservatives.
4. Releasing Agent 5.0 mL/ reagent pack – The Releasing Agent reagent contains steroid releasing agent (~0.1 µg/mL) in buffered saline with sodium azide (0.1%) and preservatives.

J. Substantial Equivalence Information:

1. Predicate device name(s):

ADVIA Centaur Testosterone Immunoassay.

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

k934562

3. Comparison with predicates:

Similarities and Differences		
Item	Candidate Device: ADVIA Centaur Testosterone (TSTO) Assay (Modified)	Predicate Devices: ADVIA Centaur Testosterone (TSTO) Assay
Intended Use	For <i>in vitro</i> diagnostic use in the quantitative determination of total testosterone (bound and unbound) in serum using the ADVIA Centaur and ADVIA Centaur XP Systems.	same
Sample Type	Serum	same
Measurement	Quantitative	same
Operating Principle	Competitive immunoassay using direct chemiluminescent technology	same
Capture Antibody	New pool of polyclonal rabbit anti-testosterone antibody bound to monoclonal mouse anti-rabbit antibody covalently coupled to paramagnetic particles.	Polyclonal rabbit anti-testosterone antibody bound to monoclonal mouse anti-rabbit antibody covalently coupled to paramagnetic particles.
Assay Range	10–1500 ng/dL (0.35–52.1 nmol/L)	same
Sample Volume	15 µL	same
Calibration	2 Point	same
Number of calibrators	Two (2) levels	same
Expected Values	241 to 827 ng/dL (male) 14 to 76 ng/dL (female)	same

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

CLSI EP05-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline

L. Test Principle:

The ADVIA Centaur Testosterone assay is a competitive immunoassay using direct chemiluminescent technology. Testosterone in the patient sample competes with acridinium ester-labeled testosterone in the Lite Reagent for a limited amount of polyclonal rabbit anti-testosterone antibody bound to monoclonal mouse anti-rabbit antibody, which is coupled to paramagnetic particles in the Solid Phase. The assay uses Testosterone Releasing Agent to release bound testosterone from the endogenous binding proteins in the sample. Unbound materials are then removed by washing. Acid Reagent and Base Reagent are then added to initiate the chemiluminescent reaction. An inverse relationship exists between the amount of testosterone 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:

A 20-day precision study was performed according to CLSI EP5-A2. Samples included human specimen pools, three levels of controls and one in-house serum control. Each sample was assayed in 2 replicates per run, 2 runs per day for 20 days for a total of 80 replicates. The results are summarized below.

Sample	Mean (ng/mL)	Within run %CV	Total %CV
Patient Pool 1	57.8	8.7	13.3
Patient Pool 1	211	4.0	7.9
Patient Pool 1	336	4.5	7.4
Patient Pool 1	574	5.5	7.1
Patient Pool 1	1096	5.1	8.5
Control Level 1	128	6.1	6.8
Control Level 2	487	5.6	8.3
Control Level 3	876	4.4	7.5
Serum Control	1167	5.7	9.1

b. *Linearity/assay reportable range:*

The linearity study of the modified ADVIA Centaur TSTO assay was performed according to CLSI EP06-A. Testing was performed on an ADVIA Centaur (XP) instrument with one lot of the modified ADVIA Centaur TSTO reagents. Nine samples for the study were prepared by serially diluting a high sample with a blank sample (charcoal-stripped human serum). These nine samples were assayed in triplicate and the mean of triplicate results was used for the analyses. Results are the following:

Sample	Expected (ng/mL)	Observed (ng/mL)	Recovery (%)	Weighted Linear Fit Estimate	Bias
A	1529.7	1529.7	100.0%	1514.4	1.0%
B	1141.8	1148.0	99.5%	1136.6	0.5%
C	781.2	766.4	101.9%	758.8	3.0%
D	347.2	384.8	90.2%	381.0	-8.9%
E	178.6	194.0	92.1%	192.1	-7.0%
F	98.9	98.6	100.3%	97.7	1.2%
G	53.8	50.9	105.7%	50.4	6.6%
H	27.5	27.0	101.8%	26.8	2.6%
I	3.2	3.2	100.0%	3.2	-0.9%

The linearity study included samples spanning the entire measuring range. The weighted linear fit regression equation is:

$$\text{Observed} = 0.99(\text{Expected}) + 0.06 \text{ ng/dL}, (r = 0.999)$$

The results from the linearity study support the measuring range of 10 ng/dL to 1500 ng/dL.

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

Traceability: The ADVIA Centaur Testosterone assay is standardized using internal standards manufactured analytically which are traceable to gas chromatography-mass spectroscopy (GCMS).

Controls: Sponsor recommends the use of commercially available quality control materials with at least 2 levels (low and high) however sponsor does not supply the controls.

Calibrators: The calibrator for the modified ADVIA Centaur TSTO assays is Calibrator E, which was previously cleared under k934562.

Stability: On-board stability for the ADVIA Centaur Testosterone (TSTO) assay was established by real time studies on the ADVIA Centaur XP system. The stability study protocol and the acceptance criteria have been found acceptable. The ADVIA Centaur Testosterone assay can be run using either the high or low volume usage option. The on board stability of the reagent for high volume usage is 7 days with a calibration interval of 16 days. The on board stability of the reagent for low volume usage is 14 days with a calibration interval of 7 days. The ADVIA Centaur Testosterone (TSTO) assay reagent is stable until the date printed on the label when stored at 2-8°C.

d. Detection limit:

The sponsor performed a detection limit study, based on CLSI EP17-A2, to determine the limit of blank (LoB) and limit of detection (LoD).

LoB determination was based on 96 determinations of blank samples obtained by testing samples in 4 replicates twice a day for 3 days. The study was run in parallel for two lots. The LoB for the modified ADVIA Chemistry TSTO assay was determined to be 3 ng/dL.

LoD determination was based on 96 determinations of low analyte samples obtained by testing samples in 4 replicates twice a day for 3 days. The study was run in parallel for two lots. The LoD for was determined to be 10 ng/dL.

The measuring range of the device is 10 – 1500 ng/dL.

e. Analytical specificity:

Interference

Interference testing for endogenous substances was performed following the guidelines of CLSI EP07-A2. Two patient serum pools, with endogenous testosterone concentrations of 90 to 110 ng/dL and 360 to 440 ng/dL were spiked with each interferent. Control samples were prepared by spiking sample pools with the appropriate diluent at the same volume as the interfering substance stock. Samples were tested in replicates of three (3) using the modified device. The sponsor defines non-significant interference as a difference of less than or equal to 5% between the spiked and the control samples. Results of non-significant interference are summarized in the table below.

Interfering Substance	Highest Concentration with non-significant interference
Hemoglobin	500 mg/mL
Triglycerides	1,000 mg/mL
Conjugated Bilirubin	20 mg/dL
Unconjugated Bilirubin	20 mg/mL

Cross Reactivity

Potential cross reactants were tested by spiking each compound into one low sample (~ 90-110 ng/dL testosterone). Testing was performed using the modified device in replicates of 6 per sample. The compounds tested, concentrations, tested, and % cross reactivity calculated are summarized below:

Cross-reactant	Concentration tested	% cross reactivity
5 α -dihydrotestosterone	100 ng/mL	5.4
Androstenedione	100 ng/mL	0.94
Methyltestosterone	100 ng/mL	0.68
Estradiol-17 β	100 ng/mL	0.02
Androsterone	1 μ g/mL	< 0.1
Cortisol	1 μ g/mL	< 0.1
Corticosterone	1 μ g/mL	< 0.1
Cyproterone	100 ng/mL	< 0.1
Danazol	1 μ g/mL	< 0.1
DHEA-sulfate	1 μ g/mL	< 0.1
11-deoxycortisol	1 μ g/mL	< 0.1
Dexamethasone	1 μ g/mL	< 0.1
Estrone	100 ng/mL	< 0.1
Oxymetholone	100 ng/mL	< 0.1
Progesterone	1 μ g/mL	< 0.1

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed by comparing the modified device to the predicate device (unmodified ADVIA Centaur TSTO assay) with 120 serum samples distributed over the assay range. The study was performed on the ADVIA Centaur XP system. Samples were run in singleton. The analysis was performed using Deming (Orthogonal) regression. The results are summarized below.

N	Regression Equation	R	Sample range (ng/mL)	Slope	y-intercept
120	$y=0.970x+7.5$	0.994	14.8 - 1304	0.970	7.5

b. Matrix comparison:

Not applicable. Serum is the only claimed sample type for the assay.

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:

The reference range previously cleared in 510(k) submission k032525 was verified following the guidelines of CLSI C28-A3c. Results of serum samples from 20 female and 20 male apparently healthy donors tested with the modified device were compared to the published claims in the Package Insert of the predicate device. The results demonstrate that the existing reference intervals for the unmodified predicate device are also applicable to the modified device. The package insert states the following for expected values for adults male and female:

241 to 827 ng/dL (male)

14 to 76 ng/dL (female)

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.