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

A. 510(k) Number:
k120009

B. Purpose for Submission:
New device

C. Measurand:
Testosterone

D. Type of Test:
Quantitative, Chemiluminescence assay

E. Applicant:
Abbott Laboratories

F. Proprietary and Established Names:
Abbott ARCHITECT 2nd Generation Testosterone

G. Regulatory Information:

1. Regulation section:
   21 CFR § 862.1680
   21 CFR § 862.1150
   21 CFR § 862.1660

2. Classification:
   Class I, reserved
   Class II
   Class I, reserved

3. Product code:
   CDZ
   JIT
   JJX

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indications for use below.

2. Indication(s) for use:
   The ARCHITECT 2nd Generation Testosterone assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of testosterone in human serum and plasma. 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.

   The ARCHITECT 2nd Generation Testosterone Calibrators are for the calibration of the ARCHITECT i System when used for the quantitative determination of testosterone in human serum and plasma.

   The ARCHITECT 2nd Generation Testosterone Controls are for the verification of the accuracy and precision of the ARCHITECT i System when used for the quantitative determination of testosterone in human serum and plasma.

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

4. Special instrument requirements:

   ARCHITECT *i* 2000_{SR} system

I. Device Description:

Each ARCHITECT 2nd Generation Testosterone Reagent Kit contains 1 bottle each of Microparticles, Conjugate, Assay Specific Diluent, and Specimen Diluent.

Microparticles (1 or 4 bottles) contain 6.6 mL Anti-Testosterone (sheep, monoclonal) coated microparticles in BIS Tris buffer with protein (bovine) stabilizer and ProClin 300 preservative.

Conjugate (1 or 4 bottles) contains 6.9 mL Testosterone acridinium-labeled conjugate in BIS Tris buffer with surfactant stabilizer and ProClin 300 preservative.

Assay Specific Diluent (1 or 4 bottles) contains 25.0 mL Testosterone Assay Diluent consisting of phosphate and glycine in citrate buffer and ProClin 300 preservative.

Specimen Diluent (1 or 4 bottles) contains 12.2 mL Testosterone Specimen Diluent consisting of PBS buffer and ProClin 300 preservative.

Each ARCHITECT 2nd Generation Testosterone Calibrator Kit contains 6 Bottles (4.0 mL each) of ARCHITECT 2nd Generation Testosterone Calibrators A-F. Calibrator A contains PBS buffer. Calibrators B through F contain testosterone (synthetic) in PBS buffer. All calibrators contain a protein (bovine) stabilizer and ProClin 300 preservative.

Each ARCHITECT 2nd Generation Testosterone Control Kit contains 3 Bottles (8.0 mL each) of ARCHITECT 2nd Generation Testosterone Controls. The Low, Medium, and High Controls contain testosterone (synthetic) in PBS buffer with a protein (bovine) stabilizer and ProClin 300 preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Roche Elecsys Testosterone II

2. Predicate 510(k) number(s):
   k093421

3. Comparison with predicate:

Similarities and Differences for Testosterone Assay		
Item	Candidate Device ARCHITECT 2nd Generation Testosterone	Predicate Device Roche Elecsys Testosterone II (k093421)
Intended Use/Indications for Use	Immunoassay for the *in vitro* quantitative determination of testosterone in human serum and plasma.	Same
Platform	ARCHITECT *i* System (immunoassay analyzer)	Elecsys and cobas e immunoassay analyzer
Methodology	Chemiluminescence (CMIA)	Electrochemiluminescence (ECLIA)
Specimen type	Serum and plasma	Same
Measuring range	4.33 – 1500 mg/dL	2.50 - 1500 ng/dL
Calibrator Levels	6	2
Control Levels	3	2

Similarities and Differences for Testosterone Calibrators		
Item	Candidate Device ARCHITECT 2nd Generation Testosterone Calibrators	Predicate Device Roche Elecsys Testosterone II (k093421)- The Elecsys Testosterone CalSetII
Intended Use/Indications for Use	For the calibration of the quantitative testosterone assay.	Same

Similarities and Differences for Testosterone Calibrators		
Item	Candidate Device ARCHITECT 2nd Generation Testosterone Calibrators	Predicate Device Roche Elecsys Testosterone II (k093421)- The Elecsys Testosterone CalSetII
Calibrator Levels	6 levels: A: 0 pg/dL B: 2.88 ng/dL C: 250 ng/dL D: 500 ng/dL E: 1,000 ng/dL F: 2,000 ng/dL	2 levels
Components	6 Bottles (4.0 mL each) of ARCHITECT 2nd Generation Testosterone Calibrators A-F. Calibrator A contains PBS buffer. Calibrators B through F contain testosterone in PBS buffer. All calibrators contain a protein (bovine) stabilizer. Preservative: ProClin 300.	Lyophilized human serum with 2 testosterone concentration levels

Similarities and Differences for Testosterone Controls		
Item	Candidate Device ARCHITECT 2nd Generation Testosterone Controls	Predicate Device Roche Elecsys Testosterone II (k093421)- The Elecsys PreciControl Universal 1 and 2
Intended Use/Indications for Use	For verification the accuracy and precision of testosterone assay.	Same
Control Levels	3 levels: Targets: Low: 8.94 Medium: 69.79 High:218.61	2 levels (multi-constituent, concentration variable on lot-to-lot basis)
Matrix and Components	3 Bottles (8.0 mL each) of ARCHITECT 2nd Generation Testosterone	Lyophilized control serum based on human serum

Similarities and Differences for Testosterone Controls		
Item	Candidate Device ARCHITECT 2nd Generation Testosterone Controls	Predicate Device Roche Elecsys Testosterone II (k093421)- The Elecsys PreciControl Universal 1 and 2
	Controls. Low, Medium, and High Controls contain testosterone in PBS buffer with a protein (bovine) stabilizer. Preservative: ProClin 300.	

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

- CLSI EP5-A2; Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition
- CLSI EP6-A; Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP7-A2; Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition
- CLSI EP9-A2-IR; Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition (Interim Revision)
- CLSI EP17-A; Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

The ARCHITECT 2nd Generation Testosterone immunoassay is based on a competitive test principle with anti-testosterone (sheep, monoclonal) coated paramagnetic microparticles and chemiluminescence detection. In the first step, sample, assay specific diluent and anti-testosterone (sheep, monoclonal) coated paramagnetic microparticles are combined. Testosterone present in the sample binds to the anti-testosterone coated microparticles. After incubation, testosterone acridinium-labeled conjugate is added to the reaction mixture. After further incubation and washing, Pre-Trigger and Trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). The concentration of testosterone is interpolated from a calibration curve established with calibrators of known testosterone concentration.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   Precision was determined following CLSI EP5-A2 guidance. Testing was

conducted using two instruments, two reagent kit lots, and one lot each of calibrators and controls. Four levels of controls and 1 human serum panel were assayed with a minimum of 2 replicates at 2 separate times per day for 20 different days. The results are summarized in the table below.

Sample	Instrument	Reagent Lot	n	Mean ng/dL	Within Run		Within - Laboratory (Total)	
					SD	%CV	SD	%CV
Control Level 1	1	1	80	9.88	0.456	4.6	0.477	4.8
		2	80	9.24	0.358	3.9	0.472	5.1
	2	1	80	9.56	0.390	4.1	0.439	4.6
		2	80	9.02	0.459	5.1	0.468	5.2
Control Level 2	1	1	80	76.07	2.339	3.1	2.734	3.6
		2	80	72.07	2.277	3.2	2.361	3.3
	2	1	80	74.24	2.492	3.4	2.661	3.6
		2	80	72.86	1.769	2.4	2.684	3.7
Control Level 3	1	1	80	228.38	4.811	2.1	5.993	2.6
		2	80	226.67	4.643	2.0	6.008	2.7
	2	1	80	227.22	5.732	2.5	7.496	3.3
		2	80	229.95	5.504	2.4	6.391	2.8
Control Level 4	1	1	80	944.73	20.617	2.2	23.101	2.8
		2	80	932.20	20.262	2.2	21.183	2.6
	2	1	80	931.44	21.325	2.3	25.752	3.2
		2	80	927.69	19.806	2.1	25.494	3.2
Panel	1	1	80	62.35	2.287	3.7	2.379	3.8
		2	80	60.72	1.285	2.1	1.796	3.0
	2	1	80	61.30	1.888	3.1	2.184	3.6
		2	80	61.53	1.558	2.5	2.028	3.3

b. Linearity/assay reportable range:

Linearity studies were performed following CLSI EP6-A guideline. Three samples were diluted to produce 3 sets of 9 evenly distributed sample pools covering assay measuring range of 4.33 to 1500 ng/dL. The linearity samples were tested with a minimum of 2 replicates on two *i* 2000_{SR} instruments over the

range of 3.82 to 1862.27 ng/dL. The measured vs. expected linear regression analysis generated a linear regression as follows: y= 0.98x + 0.12, r^2=0.998.

The data support the sponsor's claim that the measuring range for the device is 4.33 to 1500 ng/dL.

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

Traceability:
Calibrators: Abbott manufactures Testosterone internal standards (primary calibrators) gravimetrically using USP Testosterone at each concentration level. The Testosterone calibrators (market calibrators) are manufactured and tested against these internal standards.

Primary Testosterone Calibrators are prepared in a phosphate buffer synthetic matrix containing Sodium Chloride, Bovine Serum Albumin (BSA) and an antimicrobial agent. Calibrators are prepared gravimetrically to target 0, 2.88, 5.77, 46.14, 360.50, and 865.20 ng/dL Analyte containing calibrators are prepared with a 1154 ng/dL (40 nmol/L) Testosterone stock solution.

Market versions of the Testosterone Calibrators are prepared the same way as the Primary testosterone Calibrators. Each of the Market Calibrators is prepared with testosterone stock solution and 2nd Generation Testosterone Calibrator/Control Diluent to target concentrations 0, 2.88, 5.77, 46.14, 360.50, and 865.20 ng/dL (0, 0.1, 0.2, 1.6, 12.5, and 30.0 nmol/L).

Controls: Primary controls are prepared in a phosphate buffer synthetic matrix containing sodium chloride, BSA and an antimicrobial agent. Controls are prepared gravimetrically to target 8.7, 57.7, and 201.9 ng/dL (0.3, 2.0, and 7.0 nmol/L). Analyte containing controls are prepared with a 1154 ng/dL (40 nmol/L) Testosterone stock solution.

Market versions of the Testosterone Controls are prepared the same way as the Primary testosterone Controls. Each of the Market Controls is prepared with testosterone stock solution and 2nd Generation Testosterone Calibrator/Control Diluent to target to target 8.7, 57.7, and 201.9 ng/dL (0.3, 2.0, and 7.0 nmol/L)

Value assignment: The concentrations of each Market Testosterone Calibrator are determined by comparison of the relative light unit (RLU) values against the corresponding Primary Testosterone Calibrators using the ARCHITECT 2nd Generation Testosterone *i* System. The Market Calibrator is compared to the corresponding Primary Calibrator using a sample/reference ratio of the grand mean RLU results. The concentrations are adjusted, if necessary, by adding either testosterone stock solution or Calibrator A until they match the Primary Calibrator concentrations within the specification limits.

Value assignment for the Market Testosterone Controls follow the same procedure as for Market Testosterone Calibrators, please see above.

Stability: The sponsor provided the stability study protocol for reagent, calibrators and controls. The protocol and acceptance criteria were reviewed and found to be adequate. The real time stability studies are on going.
The sponsor claims shelf-life and open-vial stability 12 months for calibrators, 11 months for controls. The on board stability for the reagent is claimed to be 9 months.

d. Detection limit:

The Limit of Blank (LoB), Limit of detection (LoD) and Limit of Quantitation (LoQ) were determined in accordance with CLSI EP17-A guideline.

The zero-level samples (for determination of the LoB) and the low-level samples (for determination of the LoD) were tested with a minimum of 2 replicates for the zero-level samples and 1 replicate for the low-level samples in 5 separate runs over a minimum of 3 days. Testing was performed on 2 ARCHITECT i 2000SR instruments using 2 lots of ARCHITECT 2nd Generation Testosterone Reagents, 2 lots of ARCHITECT 2nd Generation Testosterone Calibrators and 1 lot of Controls. Samples on both instruments were tested with both reagent lots. The LoB was determined to be 1.73 ng/dL (0.06 nmol/L) and the LoD was determined to be 2.67 ng/dL (0.10 nmol/L). The LoQ is defined as the lowest analyte concentration that meets an inter-assay imprecision of < 20%. The LoQ was observed to be 4.33 ng/dL with an inter-assay CV of 15.6%.

The claimed measuring range of the device is 4.33 to 1500 ng/dL.

e. Analytical specificity:

Potential interference was evaluated following CLSI EP7-A2 guidance.

Test samples were prepared by spiking each compound at the concentration level listed in the tables into a serum sample with each level of testosterone (201.9 and 700.8 ng/dL). Reference samples were prepared by adding solvent that was used to prepare the compound stocks to a serum sample of each of the two levels of testosterone (201.9 and 700.8 ng/dL). Spiked samples and reference samples were tested in a minimum of 12 replicates on one *i* 2000SR instrument using one lot each of ARCHITECT 2nd Generation Testosterone Reagents, Calibrators, and Controls.
Results of the spiked samples were compared with the reference samples and % recovery was calculated. Non-significant interference was defined as recovery of < ±10% of control value, Based on the data the sponsor claims no significant interference for the substances and concentrations listed below.

Potentially Interfering Endogenous Substance	Highest interferent Concentrations tested
Bilirubin (unconjugated)	20 mg/dL
Bilirubin (conjugated)	20 mg/dL
Hemoglobin	500 mg/dL
Total Protein	12 g/dL
Triglycerides	2000 mg/dL
Biotin	30 ng/mL
SHBG	200 nmol/L

In addition, common pharmaceutical compounds (exogenous substances) were tested for interference at two levels of testosterone (201.9 and 700.8 ng/dL) and based on the sponsor's definition of non-significant interference ($\leq \pm 10\%$ of control value), the sponsor claims no interference for the compounds and concentrations listed in the table below.

Compounds tested	Concentrations
Acetylcystein	150 mg/L
Ampicillin	1000 mg/L
Ascorbic acid	300 mg/L
Ca-Dobesilate	200 mg/L
Cyclosporine	5 mg/L
Cefoxitin	2500 mg/L
Heparin	5000 U
Levodopa	20 mg/L
Methyldopa	20 mg/L
Metronidazole	200 mg/L

Phenylbutazone	400 mg/L
Doxycyclin	50 mg/L
Acetylsalicylic Acid	1000 mg/L
Rifampicin	60 mg/L
Acetaminophen	200 mg/L
Ibuprofen	50 mg/L
Theophilline	100 mg/L
Heparin Clexane*	5000 U
Dexamethasone	20 mg/L

* Low molecular weight heparin was used

Cross-reactivity study was performed by spiking two level testosterone serum samples (201.9 and 700.8 ng/dL) with potential cross-reactant compounds. Based on the sponsor's definition of non-significant interference (≤ ±10% of control value), the sponsor claims no cross-reactivity for the compounds and concentrations listed in the table below.

Test Compounds (Drugs)	Concentration (ng/mL)
Danazol	1,000
Dexamethasone	2,000
Ethisterone	1,000
Mestranol (17a-Ethynylestradiol 3 methyl ether)	1,000
D(-) Norgestrel	20
19-nortestosterone (Nandrolone)	30 nmol/L
Prednisolone	1,000
Prednisone	1,000
Spironolactone	500
Testosterone Propionate	100
5a-Androstane-3b,17b-diol	1,000
Androstenediol	1,000
Androstenedione	100
Cortisol	1,000
Cortisone	2,000
DHEA	1,000

DHEAS	50,000
Dihydrotestosterone	500
Epitestosterone	100 nmol/L
Estradiol (17b-Estradiol)	1,000
Estrone	1,000
Ethynodiol diacetate	50
17a-Ethynyl estradiol	1000
11b-Hydroxytestosterone	100
11-Ketotestosterone	1,000
Progesterone	1,000

Ethristone (1000 ng/mL), 11b-hydroxytestosterone (100 ng/mL), 11-ketotestosterone (1000 ng/mL), D-Norgesterel (1000 ng/mL) and 19-nortestosterone (Nandrolone, 30 nmol/L) tested above the measuring range and their percent cross-reactivity could not be calculated. Therefore, these compounds were included in the package insert,

The sponsor has the following limitations in their labeling:

"Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Specimens containing HAMA may produce anomalous values when tested with assay kits such as ARCHITECT 2nd Generation Testosterone."

"A strong interaction with D-Norgestrel (1000 ng/ml), 19-nortestosterone (Nandrolone), Ethisterone, 11b-Hydroxytestosterone, and 11-Ketotestosterone was found. Do not use samples from patients receiving these compounds."

"Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with in vitro immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous results may be observed. Additional information may be required for diagnosis."

f. Assay cut-off:

Not aplicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed according to the CLSI EP9 guideline using the Passing- Bablok regression method to compare the ARCHITECT 2nd Generation Testosterone assay to the LCMS testosterone method. A total of 138 serum samples ranging from 13.74 to 1429.61 ng/dL were used in this study. The data are summarized in the tables below.

n	ARCHITECT Testosterone (ng/dL)		LCMS (ng/dL)		Correlation Coefficient (r)		Method	Intercept		Slope	
	Min	Max	Min	Max	r	95% CL		Estimate	95% CI	Estimate	95% CI
138	13.74	1429.61	6.0	1330.0	0.994	0.992	Passing Bablok	-3.70	(-5.00, -1.66)	1.00	(0.98, 1.03)

b. Matrix comparison:

The sponsor performed a matrix comparison study using 54 sample sets. Each sample set consisted of a control tube type (Plastic serum tube) and at least one of the blood collection tubes (Glass serum tube, Plastic serum separator tube, Plastic serum separator II Advance tube and Plastic dipotassium EDTA tube) collected from one donor during one draw. Samples ranging from 14.61 to 1430.75 ng/dL were analyzed on the ARCHITECT *i* 2000 system. The samples collected in control (Plastic/Serum) tube (x) were compared to the sample from one of the paired comparator tubes (y) and the Passing/Bablok regression analysis results are summarized in the table below:

Tube type/Anticoagulant	Regression Analysis	
Glass/Serum	$y = 1.01x – 0.01$	$r^2 = 0.999$
Plastic/Serum Separator	$y = 0.98x – 0.01$	$r^2 = 0.998$
Plastic/Serum Separator II Advance	$y = 0.98x + 0.01$	$r^2 = 0.999$
Plastic/Dipotassium EDTA	$y = 1.05x – 0.01$	$r^2 = 0.998$

The sponsor claimed that serum (including serum collected in serum separator tubes) and plasma (K_2 EDTA) are acceptable collection tubes for use with the Architect 2nd Generation Testosterone 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 expected ranges for the ARCHITECT 2nd Generation Testosterone assay were obtained from testing a minimum of 120 samples from apparently healthy individuals in the following categories: normal males, 21-49 years of age with an intact reproductive system, and normal females 21-49 years of age. Additional samples were tested from apparently healthy males and females (> 50 years of age). The data are summarized in the table below.

Category Apparently healthy	n	Age Range (years)	Testosterone (ng/dL)				
			Median	Min.	Max.	5^{th} percentile	95^{th} percentile
Males (21-49 years of age)	129	21-49	494.03	47.01	980.56	240.24	870.68
Males (> 50 years of age)	71	50-77	442.41	127.18	1020.36	220.91	715.81
Females (21-49 years of age)	129	21-49	24.80	7.21	79.31	13.84	53.35
Females (> 50 years of age)	52	50-82	23.50	8.65	36.92	12.40	35.76

It is recommended that each laboratory establish its own reference range that is appropriate for the laboratory's patient population (i.e., a normal range that reflects the type of specimen and demographic variables such as age and sex, as applicable).

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.