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

A. 510(k) Number:

k151529

B. Purpose for Submission:

New device

C. Measurand:

Total Testosterone

D. Type of Test:

Quantitative Chemiluminescent Immunoassay

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Dimension Vista LOCI Total Testosterone Flex reagent cartridge

Dimension Vista Testosterone Calibrator

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1680, Testosterone Test System

   21 CFR 862.1150, Calibrator

2. Classification:

   Class I, reserved

   Class II

3. Product code:

   CDZ

   JIT

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below

2. Indication(s) for use:

   The Dimension Vista LOCI Total Testosterone Flex reagent cartridge is an in vitro diagnostic test for the quantitative measurement of total testosterone in human serum and plasma on the Dimension Vista 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.

   The Dimension Vista Testosterone Calibrator is an in vitro diagnostic product for the calibration of the Total Testosterone (TTST) assay on the Dimension Vista System.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   The assay is intended for use on the Dimension Vista System

I. Device Description:

The Dimension Vista LOCI Total Testosterone Flex reagents are liquid and are contained in reagent wells of a Flex reagent cartridge. There are twelve wells in each Flex reagent cartridge. The reagents for the assay are assigned to wells as described below:

Wells 1 through 4 each contain 31.3 ng/mL Testosterone biotinylated antibody reagent (sheep monoclonal) at a concentration of 31.3 ng/mL testosterone and 1200 ng/mL of displacer, as well as buffers, stabilizers and preservatives.

Wells 5 through 8 each contain 100 µg/mL of Testosterone Chemibead Reagent, as well as buffers, stabilizers and preservatives.

Wells 9 through 12 each contain 400 µg/mL of Testosterone Sensibead Reagent, as well as buffers, stabilizers and preservatives.

The Dimension Vista Testosterone Calibrator (TTST CAL) is a lyophilized human serum based calibrator set containing testosterone and preservatives. Within each set of twelve vials there are two 1.0 mL amber glass vials for each calibrator level. There are six calibrator levels, labeled A-F, which span the assay range. The total testosterone concentrations of the six levels are listed below:

Calibrator A: 0 ng/dL
Calibrator B: 20 ng/dL
Calibrator C: 50 ng/dL
Calibrator D: 100 ng/dL
Calibrator E: 200 ng/dL
Calibrator F: 1100 ng/dL

The calibrator material contains human source material. Each donor unit used in the preparation of this product was tested by FDA-approved methods for the presence of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2), as well as for Hepatitis B surface Antigen and antibody to Hepatitis C Virus (HCV), and found to be negative (not repeatedly reactive).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Elecsys Testosterone II Assay

   Roche Elecsys Testosterone Calset II

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

   k093421

   k003411

3. Comparison with predicate:

Assay

Similarities		
Item	Candidate Device Dimension Vista LOCI Total Testosterone Flex Reagent Cartridge (k151529)	Predicate Device Roche Elecsys Testosterone II Assay (k093421)
Intended Use	In vitro diagnostic test for the quantitative measurement of total testosterone in human serum and plasma.	Same
Method	Competitive immunoassay	Same
Antibodies	Sheep monoclonal	Same

Differences		
Item	Candidate Device Dimension Vista LOCI Total Testosterone Flex Reagent Cartridge (k151529)	Predicate Device Roche Elecsys Testosterone II Assay (k093421)
Technology	Chemiluminescent LOCI	Electrochemiluminscence ECLIA
Sample size	10 µL	20 µL
Sample type	Serum, Lithium Heparin plasma, Na Heparin plasma, K2-EDTA plasma.	Serum, Lithium Heparin plasma, K2- and K3-EDTA plasma.
Measuring range	8.0- 1000 ng/dL	2.5-1500 ng/dL

Calibrators

Similarities and Differences		
Item	Candidate Device Dimension Vista Testosterone Calibrator (k151529)	Predicate Device Roche Elecsys Testosterone Calset II (k003411)
Intended use	An in vitro diagnostic product for the calibration of the testosterone assay.	Same
Calibrator form	Lyophilized	Same
Calibrator matrix	Human serum	Same
Traceability	ID-LC/MS/MS (CDC reference method)	ID-GC/MS
Levels	Six:	Two:

Similarities and Differences		
Item	Candidate Device Dimension Vista Testosterone Calibrator (k151529)	Predicate Device Roche Elecsys Testosterone Calset II (k003411)
	Calibrator A: 0 ng/dL Calibrator B: 20 ng/dL Calibrator C: 50 ng/dL Calibrator D: 100 ng/dL Calibrator E: 200 ng/dL Calibrator F: 1100 ng/dL	Calibrator 1: <1.0 ng/mL Calibrator 2: 13.0 ng/mL

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

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

CLSI EPO5-A2, Evaluation of Precision Performance of Clinical Chemistry Devices, Approved Guideline, Second Edition

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

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

CLSI EP07-A2, Interference Testing in Clinical Chemistry, Approved Guideline, Second Edition

CLSI EP09-A3, Measurement Procedure 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 EP32-R, Metrological Traceability and Its Implementation, A Report; February 17, 2006.

L. Test Principle:

The Dimension Vista LOCI Total Testosterone (TTST) Flex method is a homogeneous, competitive chemiluminescent immunoassay based on LOCI technology. LOCI reagents include two synthetic bead reagents and labeled testosterone antibody. The first bead reagent (Chemibeads) is coated with a testosterone analog and contains a chemiluminescent dye.

The second bead reagent (Sensibeads) is coated with streptavidin and contains photosensitive dye. Chemibeads and labeled testosterone antibody are added sequentially to the reaction vessel. Testosterone from the patient sample competes with the testosterone-analog-chemibeads for a limited amount of labeled testosterone antibody. Sensibeads are then added and bind to the biotinylated portion of the labeled testosterone antibody to form bead pair immunocomplexes. Illumination of the complex by light at 680 nm generates singlet oxygen for the Sensibeads which diffuses to the Chemibeads triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is an inverse function of the concentration of total testosterone in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision testing was performed in accordance with CLSI EP05-A2 guidance. Three serum and one plasma pools, and three levels of human serum based commercial controls were run using one reagent lot and one analyzer in duplicate, twice a day for 20 days for a total of 80 measurements per sample. A result summary of the precision study is shown in the table below:

		Within-Run		Total (n=80)	
Sample	Mean (ng/dL)	SD	%CV	SD	%CV
Serum 1	13	0.7	5.2	1.0	7.3
Serum 2	75	1.4	1.9	1.6	2.1
Serum 3	767	13.8	1.8	18.2	2.4
Li-heparin Plasma	384	14.3	3.7	15.8	4.1
Control 1	71	1.2	1.7	1.8	2.6
Control 2	441	4.1	0.9	5.6	1.3
Control 3	855	13.2	1.6	16.9	2.0

b. Linearity/assay reportable range:

Linearity studies were performed for serum and Li-heparin, Na-heparin, and K2-EDTA plasma samples. One high sample and one low pool for each sample type were combined in varying ratios to produce ten dilutions across the claimed measuring range of 8.0 to1000 ng/dL. The expected values were calculated based on the dilution factor used. The following linear regression equations were obtained:

Serum: $y=0.97x + 0.1$, $R^2=0.998$

Li-Heparin: $y= 0.98x + 0.0$, $R^2=0.999$

Na-Heparin: $y= 0.98x + 0.1$, $R^2=0.996$

K2-EDTA: $y= 0.96x + 0.1$, $R^2=0.999$

The linearity data supports the claimed measuring range of 8.0-1000 ng/dL.

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

Traceability: The Dimension Vista Testosterone Calibrator is traceable to a primary reference method, CDC Reference Method: ID-LC/MS/MS. Traceability was verified by serum sample method comparison on the Dimension Vista against the CDC reference method, ID-LC/MS/MS.

The sponsor has obtained certification in the CDC Hormone Standardization (HoST) program. Please see CDC Hormone Standardization program at http://www.cdc.gov/labstandards/hs.html.

Value Assignment: Each lot of calibrator is assigned during manufacturing with a Testosterone Masterpool, which is traceable to CDC ID-LC/MS/MS. The lot value assignment of the calibrators are determined by measuring 5 replicates of each calibrator, during 3 runs, over 3 days, using 3 reagent lots and 3 analyzers. The calibrator results must meet internal specifications before release. The calibrator target concentrations are as follows:

Level A: 0 ng/dL
Level B: 20 ng/dL
Level C: 50 ng/dL
Level D 100 ng/dL
Level E: 200 ng/dL
Level F: 1100 ng/dL

Stability: Real-time open-vial and shelf-life stability studies were performed to determine the stability of the Dimension Vista Testosterone Calibrator. The study protocol and acceptance criteria were reviewed and found to be acceptable. The stability studies support the sponsor's shelf-life stability claim of 12 months when stored at -15 to -25^{o} C. Once reconstituted, the calibrators are stable for 14 days when stored on board the Dimension Vista System. Reconstituted calibrators are stable for 30 days when recapped immediately after use and stored at 2-8^{o}C.

The sponsor recommends the use of commercially available control material in the package insert labeling.

d. Detection limit:

Limit of Blank (LoB):

The LoB was estimated using a nonparametric approach. Six blank samples (testosterone stripped serum) were tested on three reagent lots on one analyzer over three days, for a total of 90 measurements. The LoB for each lot was taken as the rank position at the 95^{th} percentile calculated from the following equation, Rank position= 0.5 + 0.95B, where B = total number of replicates. The largest result across lots was taken as the LoB. The LoB was determined to be 1.1 ng/dL.

Limit of Detection (LoD):

The LoD was calculated parametrically for each of three reagent lots using 8 individual serum samples with low endogenous testosterone (0.6 to 8.5 ng/dL). For each reagent lot tested, 120 replicate determinations were made over three days. The LoD was calculated using the following equation: $LoD = LoB + c_p SD_{L,}$ where c_p is a multiplier to give the 95^{th} percentile of a normal distribution and L is the total number of all low level ample results across all reagent lots. The maximum observed LoD across all reagent lots was taken as the LoB estimate value. The LoD was determined to be 2.4 ng/dL.

Limit of Quantitation (LoQ):

The LoQ was determined using 8 individual low-level serum samples (0.6-8.5 ng/dL) and 5 low-level plasma samples for each plasma sample type (Li-Hep, Na-Hep, K2-EDTA). All sample types were analyzed in duplicate, twice a day for 20 days for a total of 80 measurements per sample. The LoQ is defined as the lowest analyte concentration that can be reproducibly measured with a total precision CV of $\leq 20\%$.

The maximum LoQ for two lots tested for serum was 4.5 ng/dL

The maximum LoQ for the two lots tested for sodium-heparin and lithium-heparin sample types was 6.0 g/dL; and for the K2- EDTA sample type was 5.0 ng/dL

The sponsor lists the following detection limits in the assay package insert labeling:

LoB	LoD	LoQ
4.0 ng/dL	5.0 ng/dL	8.0 ng/dL

The claimed measuring range of the assay is 8.0 to 1000 ng/dL

e. Analytical specificity:

Interference:
The Testosterone assay was evaluated for interference according to CLSI EP7-A2. Hemolysis, icterus, and lipemia and several specific interferents were tested using a

paired-difference approach. Serum and plasma samples containing the substance to be tested and control sample not containing the substances were spiked with approximately 50 and 300 ng/dL of testosterone. Five replicates were tested for each test and control sample. The sponsor defines significant interference as greater than 10% difference in the test sample results as compared to the control samples. The results are summarized in the table below:

Substance	Highest Tested Concentration at which no significant interference (≤±10%) was observed
Hemoglobin	1000 mg/dL
Bilirubin (unconjugated)	60 mg/dL
Bilirubin (conjugated)	60 mg/dL
Lipemia (intralipid)	1000 mg/dL
Acetaminophen	20 mg/dL
Acetylcysteine	150 mg/L
Amikacin	8 mg/dL
Ampicillin	5.3 mg/dL
Ascorbic Acid	6 mg/dL
Biotin	100 µg/mL
Calcium Dobesilate	200 mg/dL
Caffeine	6 mg/dL
Carbamazepine	3 mg/dL
Cefoxitin	2500 mg/dL
Chloramphenicol	5 mg/dL
Chlordiazepoxide	1 mg/dL
Chlorpromazine	0.2 mg/dL
Cholesterol	503 mg/dL
Cimetidine	2 mg/dL
Creatinine	30 mg/dL
Cyclosporine	5 mg/L
Dextran 40	5000 mg/dL
Diazepam	0.51 mg/dL
Digoxin	6.1 ng/mL
Doxycycline	50 mg/L
Enoxaparin Sodium	60 mg/L
Erythromycin	6 mg/L
Ethanol	400 mg/dL
Ethosuximide	25 mg/dL
Furosemide	6 mg/dL
Gentamicin	1 mg/dL
Heparin	3 U/mL
Ibuprofen	50 mg/dL

Immunoglobulin G	4 g/dL
Levodopa	20 mg/L
Lidocaine	1.2 mg/dL
Lithium	2.2 mg/dL
Leuprolide	200 ng/mL
Methyldopa	20 mg/L
Metronidazole	200 mg/L
Nicotine	0.1 mg/dL
Penicillin G	25 U/mL
Pentobarbital	10 mg/dL
Phenobarbital	15 mg/dL
Phenylbutazone	400 mg/dL
Phenytoin	5 mg/dL
Primidone	4 mg/dL
Propoxyphene	0.16 mg/dL
Protein, albumin	5 g/dL
Protein, total	10.5 g/dL
Rheumatoid Factor	1110 IU/mL
Rifampicin	60 mg/L
Salicylic Acid	60 mg/dL
Theophylline	4 mg/dL
Triglycerides	900 mg/dL
Urea	500 mg/dL
Uric Acid	20 mg/dL
Valproic Acid	50 mg/dL
Vancomycin	10 mg/dL

The sponsor includes the following interference limitations in the assay package insert labeling:

Albumin at 6 g/dL decreased TTST results by 19% at a testosterone concentration of 50 ng/dL.

Immunoglobin G at 5 ng/dL increased TTST results 27% at a testosterone concentration of 300 ng/dL.

Triglycerides at 1000 mg/dL decreased TTST results by 11% at a testosterone concentration of 300 ng/dL.

Cross-Reactivity:
The following substances in the amounts indicated in the table below were evaluated and found to have insignificant cross reactivity with the TTST method when present in serum and plasma containing 0 ng/dL and 300 ng/dL testosterone. The sponsor defines significant cross reactivity as a bias in results greater to or equal to 10%.

The percent cross-reactivity was calculated as follows:

$$\% \text{ Cross Reactivity} = \frac{[\text{measured TTST conc.}]-[\text{control TTST conc.}]}{[\text{cross reactant conc.}]} \times 100$$

Substance	Substance concentration (ng/mL)	Maximum % Cross Reactivity
5α-dihydro-testosterone	500	0.3
5α-Androstane-3β,17β-diol	1000	-0.03
5-androstene-3β,17β-diol	1000	0.2
5 β -androstene-3β,17β-diol	100	-0.2
11 β- hydroxytestosterone	1000	1.9
11-dexoycortisol	1000	0.01
11-ketotestosterone	1000	1.6
17 α-methyltestosterone	100	4.2
17 β-estradiol	1000	-0.02
Andostenedione	100	0.2
Androsterone	1000	0.004
Corticosterone	1000	0.001
Cortisol	1000	0.01
Danazol	1000	0.1
Dehyroepiandosterone	1000	-0.01
DHEA-Sulfate	50000	0.03
Dexamethasone	2000	0.003
Esterone	1000	-0.01
Ethisterone	1000	0.1
Norethindrone	50	0.5
Norgestrel	1000	0.1
Oxymetholone	100	0.02
Progesterone	1000	0.0
Testosterone propionate	100	0.0
Prednisone	1000	0.01
Prednisolone	1000	-0.002
Cortisone	2000	0.003

The sponsor includes the following cross-reactivity claims in the assay package insert labeling:

“Nandrolone decanoate (19-nortestosterone) shows significant cross-reactivity with the TTST assay. Do not use samples from patients under Nandrolone treatment.”

HAMA interference study:
Human anti-mouse antibodies (HAMA) interference was evaluated according to CLSI EP07-A2 guideline. Samples tested consisted of individual human serum samples with low and high endogenous HAMA. The samples were spiked with two levels of testosterone, approximately 150 ng/dL and 700-800 ng/dL testosterone. The sponsor defined significant interference as ≥ ±10% difference between the tested sample and the control sample. Five replicates were run on each sample. The results are summarized in the table below:

HAMA Concentration	Testosterone Level	% Interference
1248 ng/mL	149 ng/dL	-4%
285 ng/mL	156 ng/dL	-2%
1248 ng/mL	887 ng/dL	-6%
285 ng/mL	746 ng/dL	-5%

The sponsor includes the following limitation in the labeling regarding heterophilic antibody (HAMA) interference:

"Patient samples may contain heterophilic antibodies, of which human anti-mouse antibodies (HAMA) are the most commonly encountered. Heterophilic antibodies such as HAMA may cause falsely decreased or elevated results in immunoassay tests. Siemens characterized the impact of HAMA in accordance with CLSI EP7-A2 and this testing indicated ≤ 10% bias with the TTST assay. While the TTST reagent has been designed to mitigate interference from heterophilic antibodies, complete elimination of these interferences from all patient specimens cannot be guaranteed. A test result that is inconsistent with the patient's clinical presentation and history should be interpreted with caution."

The sponsor includes the following literature references in the labeling regarding interference from other patient specific interferents such as anti-dextran or anti-streptavidin antibodies:

1. Ismail AA, Walker PL, Cawood ML and Barth JH: Interference in immunoassay is an underestimated problem. Ann. Clin. Biochem 2002; 39; 366-373.
2. Rulander NJ, Cardamone D, Senior M, et. al. Interference from Anti-Streptavidin Antibody. Arch Pathol Lab Med 2013; 137: 1141-1146.
3. Anastase S. et al, Affinity chromatography of human anti-dextran antibodies. Isolation of two distinct populations. J Chromatogr B Biomed Appl. 1996 Nov 15; 686(2):141-50.
4. Larsson A. et al, Destruction of dextran-coated target cells by normal human lymphocytes and monocytes. Induction by a human anti-dextran serum with IgG antibodies restricted to the IgG2 subclass. Scand J Immunol. 1975; 4(3):241-52.

5. Kennel A. et al, Serum anti-dextran antibodies in IgA nephropathy. Clin Nephrol. 1995 Apr; 43(4):216-20.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was conducted to compare the Dimension Vista TTST assay to the predicate device, the Roche Elecsys Testosterone II assay. Two-Hundred and fifteen (215) unaltered patient serum samples were tested using one reagent lot. The sample results on the candidate device ranged from 11.0 to 982 ng/dL. Passing Bablok was used to analyze the data and the following regression data was obtained:

y= 0.90x - 2.6, r=0.99

The slope showed an approximate bias of -10% between the candidate device and the predicate device; however, this shift is expected because the purpose of the device modification was to adjust the calibration to better align with the CDC reference sample concentration target levels. Therefore, test results from the candidate device do not, and are not expected to, directly correlate with test results from the predicate device.
An additional method comparison study was conducted to evaluate the accuracy between the candidate device and the CDC reference method. The method comparison against the CDC reference method was the basis of the substantial equivalence determination.

A method comparison study was performed between the Dimension Vista TTST assay and the CDC reference method, ID-LC/MS/MS. One hundred thirteen (113) native serum samples were run in singlet on the candidate and comparator methods. The test results as measured by the candidate device ranged from 8.0 to 949 ng/dL. Regression analysis was performed using Passing-Bablok to obtain the following regression equation:

Slope	95% CI	Intercept	95% CI	r	n
0.93	0.92-0.95	4.0	0.4-5.7	0.994	113

b. Matrix comparison:

Fifty nine sample sets were collected and analyzed by Deming weighted regression to compare testosterone results obtained from serum to serum collected in a serum separator tube (SST), Li-Heparin plasma, Na-Heparin plasma, and K2-EDTA plasma. Results from the serum samples ranged from 12 to 924 ng/dL. The regression equations are summarized in the following table:

Comparative Sample type to Serum (n=59)	Slope	Intercept	Correlation coefficient
Li-Hep plasma	0.98	-1.6	0.998
Na-Hep plasma	0.99	-1.4	0.996
K2-EDTA plasma	1.00	-1.1	0.998
SST serum	0.97	-0.7	0.995

The matrix comparison study results support the use of SST serum, Li-heparin, Na-heparin, and K2-EDTA plasma with this 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:

   A reference interval study was performed for the Dimension Vista LOCI Total Testosterone assay. The sample groups tested consisted of males, > 50 years old (n=146); males between the ages of 21 to 50 years old (n=174); post-menopausal females, ages 48 to 85 years (n=146); and pre-menopausal females, ages 21 to 60 years (n=189). The central 95th percentile range of each sample category was calculated by finding the 2.5th ranked sample on the low end and the 97.5th ranked sample on the high end. The follow reference intervals were obtained for each category:

   Adult males (21 to 50 yrs): 113 to 1065 ng/dL

   Adult males (>50 yrs): 95 to 948 ng/dL

   Pre-menopausal females: 9 to 53 ng/dL

Post-menopausal females: <8 to 48 ng/dL

A reference range study was performed on the pediatric population following CLSI EP28-A3c. Male and female pediatric patient samples were obtained spanning multiple age ranges and Tanner Stages. Serum specimens were obtained prospectively at eight sites located across the US. Each category of samples was analyzed separately. The reference intervals are presented in tables below for both Tanner Stages and age range:

Male Pediatric Reference Ranges According to Tanner Stage

Tanner Stage	Gender	N	Lower 2.5% (ng/dL)	Upper 97.5% (ng/dL)
Stage I	Male	39	<8	64
Stage II	Male	41	<8	166
Stage III	Male	42	<8	609
Stage IV	Male	42	43	756
Stage V	Male	42	66	841

Female Pediatric Reference Range According to Tanner Stage

Tanner Stage	Gender	N	Lower 2.5% (ng/dL)	Upper 97.5% (ng/dL)
Stage I	Female	45	<8	79
Stage II	Female	41	<8	45
Stage III	Female	39	<8	49
Stage IV	Female	40	8	54
Stage V	Female	41	14	71

Male Pediatric Reference Ranges According to Age

Age	Gender	N	Lower (ng/dL)	Upper (ng/dL)
2-10 years	Male	44	<8	31
11 years	Male	21	<8	321
12 years	Male	24	<8	531
13 years	Male	20	<8	609
14 years	Male	30	23	652
15 years	Male	20	126	792
16-21 years	Male	44	116	779

Female Pediatric Reference Ranges According to Age

Age	Gender	N	Lower (ng/dL)	Upper (ng/dL)
2-10 years	Female	40	<8	80
11-15 years	Female	125	<8	49
16-21 years	Female	35	20	56

Data Analysis: Each category of samples was analyzed separately. Due to the limited

availability of pediatric samples, the sample analysis method varied depending on the number of samples in each subgroup. The table below shows the relative percentiles reported based on available sample number.

Number of Samples	Percentile Reported	Calculation Method
19≤N≤38	5^{th} and 95th (Central 90^{th})	Non-parametric
N=39	2.5^{th} and 97.5^{th} (Central 95th)	Non-parametric
40≤N≤119	2.5^{th} and 97.5^{th} (Central 95^{th})	Robust measure of location and spread, Horn PS, Pesce AJ Referenence Intervals: A Users Guide. Washington, DC: AACC Press; 2005
N≥120	2.5^{th} and 97.5^{th} (Central 95^{th})	None-parametric in accordance with CLSI guideline EP28-A3, Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory: Approved Guideline, 3^{rd} edition.

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.