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

A. 510(k) Number:

k093441

B. Purpose for Submission:

New assay

C. Measurand:

Digoxin

D. Type of Test:

Homogeneous quantitative immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Dimension Vista® LOCI Digoxin Flex® reagent cartridge; Dimension Vista® DRUG 4 Calibrator

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.3320 and 21 CFR 862.3200

2. Classification:

   Class II

3. Product code:

   KXT (assay), DLJ (calibrator)

4. Panel:

   91, Toxicology

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The DIGXN method is an in vitro diagnostic test for the quantitative measurement of digoxin in human serum and plasma on the Dimension Vista® System. Measurements of digoxin are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to help ensure appropriate therapy.

   Calibrator

   The DRUG 4 CAL is an in vitro diagnostic product for the calibration of the LOCI Digoxin (DIGXN) method on the Dimension Vista® System.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Dimension Vista® System. The 510(k) demonstrates assay performance on the Dimension Vista 1500.

I. Device Description:

Reagent components are shown in the table below.

Reagents	Wells	Form	Ingredient	Source
1	1-4	Liquid	Biotinylated Anti-Digoxin F(ab′)2	Mouse, monoclonal
2	5-8	Liquid	Ouabain-EDA Chemibeads with buffers, stabilizers,	
3	9-12	Liquid	Streptavidin Sensibeads	Recombinant *E. coli*

The DRUG 4 Calibrator is a 5 level, liquid calibrator. The product matrix is human serum. Target levels are 0.00, 0.60, 1.25, 2.50, and 5.30 ng/mL. 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 (HBsAg) and antibody to Hepatitis C Virus (HCV), and found to be negative (not repeatedly reactive). The sponsor includes the precaution in the labeling that because no testing can offer complete assurance that these or other infectious agents are absent, this material should be handled using good laboratory practice to avoid skin contact and ingestion.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Digoxin Flex Reagent Cartridge; Dimension Drug Calibrator

2. Predicate 510(k) number(s)

   k946153; k011035

3. Comparison with predicate:

   The assays have the same intended use. Differences in assay methodology are listed below:

Feature	**Dimension Vista® LOCI DIGXN Flex® reagent cartridge**	**Predicate Dimension® DGNA Flex® reagent cartridge**
Indications for use	Measurements of digoxin are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to help ensure appropriate therapy	Same
Assay Type	Chemiluminescent immunoassay based on LOCI® technology	Affinity particle mediated immunoassay
Measurement	measurement at 612 nm	Bichromatic rate (577 and 700 nm)
Antibody	Monoclonal Mouse Antibody	Rabbit Antibody
Feature	**Dimension Vista Drug 4 Calibrator**	**Dimension Drug Calibrator**
Indications for use – calibrators	For the calibration of the LOCI Digoxin method on the Dimension Vista System	For the calibration of drug methods (digoxin, lithium, phenobarbital, phenytoin and theophylline) on the Dimension Vista System.

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

CLSI documents referenced include: "Evaluation of Precision Performance of Clinical Chemistry Devices", EP5; "Evaluation of the Linearity of Quantitative Measurement", EP6; "Method Comparison and Bias Estimation Using Patient Samples", EP9, "Protocols for Determination of Limits of Detection and Limits of Quantitation", EP 17.

L. Test Principle:

The DIGXN method is a homogeneous, sequential, chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead

reagents and a biotinylated F(ab′)2 fragment of an anti-digoxin mouse monoclonal antibody. The first bead reagent (Chemibeads) is coated with ouabain, a weaker binding analog of digoxin, and contains a photosensitizer dye. In a first step, sample is incubated with biotinylated F(ab′)2 which allows digoxin from the sample to saturate a fraction of the biotinylated F(ab′)2 that is directly related to the digoxin concentration. In a second step, ouabain chemibeads are added and form bead/biotinylated F(ab′)2 immunocomplexes with the nonsaturated fraction of the biotinylated F(ab′)2. Sensibeads are then added and bind to the biotin to form bead pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is an inverse function of the digoxin concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision

Precision was evaluated for (i) human serum samples containing 0.92 ng/mL and 2.44 ng/mL digoxin and (ii) commercial serum-based QC products. Testing was performed daily for 20 days. During each day of testing, 2 test samples of each test materials were analyzed in two separate runs. The evaluation was performed with one reagent lot, one instrument and one calibration.

The standard deviations (SD) and percent coefficient of variation (% CV) shown in the table below were calculated by the analysis of variance (ANOVA) method in accordance with CLSI Guideline EP5-A2.

Material	Mean (ng/mL)	Repeatability SD	Repeatability %CV	Within Lab SD	Within Lab %CV
Control material					
Level 1	0.67	0.01	1.5	0.01	1.7
Level 2	1.63	0.02	1.2	0.02	1.4
Level 3	3.31	0.05	1.4	0.05	1.5
Serum					
Level 1	0.92	0.01	1.5	0.02	1.7
Level 2	2.44	0.03	1.3	0.03	1.4

An additional (20 day) precision evaluation was performed for samples spiked at 0.10 ng/mL digoxin. Estimated within-lab CV in this evaluation was 7%.

Precision at the upper end of the range was assessed using a 4.5 ng/mL digoxin sample, over 5 days. On each day, there was one run per day and 5

replicates per run. In this evaluation the within–lab CV estimate at this concentration was 1.1%.

b. Linearity/assay reportable range:

The sponsor's claimed analytical measuring range of the Dimension Vista® LOCI DIGXN Flex® reagent cartridge assay is 0.06 – 5 ng/mL. This is supported by the linearity evaluation as well as performance at the assay lower limits (see detection limit, below). Linearity was confirmed by testing 9 levels of serum pools and comparing observed versus expected values. The study design followed CLSI Guideline EP-6. The high pool was prepared gravimetrically using USP material; intermediate dilutions were prepared by combining high and low pools. The pools were assayed using the LOCI DIGXN method. The means (N=5) of the observed values for each sample were plotted versus the expected values. Linear regression yielded: y= 0.98X+0.03, R^2=0.998. Results in terms of recovery are shown in the table below:

Observed digoxin value (ng/mL)	Expected digoxin value (ng/mL)	Difference	Percent difference
0.03	0.00	0.03	N/A
0.71	0.71	-0.02	-3.0
1.42	1.42	-0.04	-3.0
2.13	2.13	0.00	-0.1
2.84	2.84	0.09	3.0
3.55	3.55	0.05	1.3
4.27	4.27	0.01	0.3
4.98	4.98	-0.19	-3.9

The package insert recommends that samples above the measuring range may be diluted with zero calibrator. To evaluate recovery using this procedure spiked sample, and native patient samples were diluted using this. Results are shown below. Measurements of all diluted samples showed recovery within +/- 10% of the expected value, and no significant trends were observed.

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

Calibrator value assignment and estimation of uncertainty:
Values are assigned to new lots from a master pool that is referenced to the United States Pharmacopoeia material for digoxin. The estimates of uncertainty for calibrator value assignment were described in the 510(k) taking into account the uncertainty of the USP digoxin, the gravimetric and volumetric processes, and the variability of the value assignment process used to assign the product calibrators. The statistical approach followed EUROCHEM/CITAC Guide to Measurement Uncertainty and the Guide to

Uncertainty of Measurement prepared by ISO. The uncertainty of the product calibrator described in the 510(k) is ≤ 2%.

Stability:
Target shelf life for the Dimension Vista Drug 4 Calibrator is determined by comparing results of test product stored at recommended conditions with control samples stored at -20 and -70 degrees C. Recovery is monitored for trends at multiple time points across the expiration dating period, and percent change over time is determined. No significant drift was observed in calibration for the 30 day open vial stability study. The manufacturer's acceptance criteria for is ≤ 4% for shelf life stability and ≤ 5% for open vial stability for levels B-E. The criterion for level A is < 0.06 ng/mL.

d. Detection limit:

The manufacturer's claimed limit of detection (LoD) for the Dimension® Vista LOCI Digoxin (DIGXN) method is 0.06 ng/mL. This was determined consistent with CLSI guideline EP17, and with false positives (α) and false negatives (β) less than 5%, based upon 240 determinations with 120 blank and 120 low level samples. The low concentration patient samples used for the LoD study were unaltered (native) human serum samples. Values for individual samples were determined using a DIGXN Flex® lot. Results support the LoD of 0.06 ng/mL.

To determine total analytical error at the limit of detection, three low level (0.06 ng/mL) serum samples were prepared by spiking normal human serum with digoxin master pool prepared from USP material to 0.06 ng/mL digoxin (determined gravimetrically). Samples were tested on two different Dimension Vista® instruments using two different DIGXN Flex® reagent lots, over 3 runs, with three replicates per run. A total of 54 measurements were performed.

The standard deviations for a sample with concentration 0.06 ng/mL (gravimetrically determined) ranged from 0.006 to 0.008 (0.0068 average) ng/mL. Bias ranged from 0.006 to 0.009 (0.0075 average) at this level. Total analytical error was estimated as 0.021 at 0.06 ng/mL or 30%.

e. Analytical specificity:

To evaluate interference test samples were prepared by spiking each potential interferent into aliquots of serum sample pools at digoxin concentrations of 0.40 ng/mL and 2.00 ng/mL. The test samples were analyzed as patient samples and the results were compared to control samples (containing only digoxin without the potential interfering substances.

The endogenous compounds and the concentration at which they were tested are shown below:

Endogenous compound	Concentration	Mean percent bias in presence of 0.4 ng/mL Digoxin	Mean percent bias in presence of 2.0 ng/mL Digoxin
Bilirubin - conjugated	20 mg/dL	7.6	4.0
Bilirubin - unconjugated	20 mg/dL	3.8	1.6
Cholesterol	503 mg/dL	5.9	1.3
Gamma-Globulin	5000 mg/dL	-4.5	-4.7
Hemoglobin	1000 mg/dL	-9.0	-9.9
Protein, albumin	6000 mg/dL	-1.0	-1.6
Protein, total	12,000 mg/dL	-3.5	-3.2
Rheumatoid Factor	707 IU/L	1.6	-0.3
Triglycerides	3000 mg/dL	-1.9	-0.9
Uric Acid	20 mg/dL	7.6	3.1

The following substances were evaluated for cross-reactivity with the DIGXN method when present in serum containing 0.00 ng/mL and 2.00 ng/mL of digoxin in the amounts indicated. The percent cross-reactivity was calculated as follows:
% Cross-reactivity = [measured analyte] - [control analyte] x 100/[metabolite]

Substance	Digoxin Level Tested ng/mL	Cross-Reactivity %
Acetyldigitoxin (25 ng/mL)	0	14
	2.00	10
Deslanoside (2.5 ng/mL)	0	56
	2.00	63
Digitoxin (25 ng/mL)	0	13
	2.00	10
Digoxigenin (5 ng/mL)	0	8
	2.00	-9
Digoxigenin bis-digitoxoside (2.5 ng/mL)	0	96
	2.00	94
Digoxigenin mono-digitoxoside (2.5 ng/mL)	0	59
	2.00	52

Dihydrodigoxin (25 ng/mL)	0	2
	2.00	-3
Gitoxin (25 ng/mL)	0	0
	2.00	-1
Lanatoside C (1.5 ng/mL)	0	59
	2.00	70

A list of all exogenous compounds and concentrations at which they were tested is included in the package insert. No change in recovery > 10% was observed with any of the other compounds tested. In most cases recoveries were well-within this criterion.

f. Assay cut-off:

Not applicable – this is a quantitative test.

2. Comparison studies:

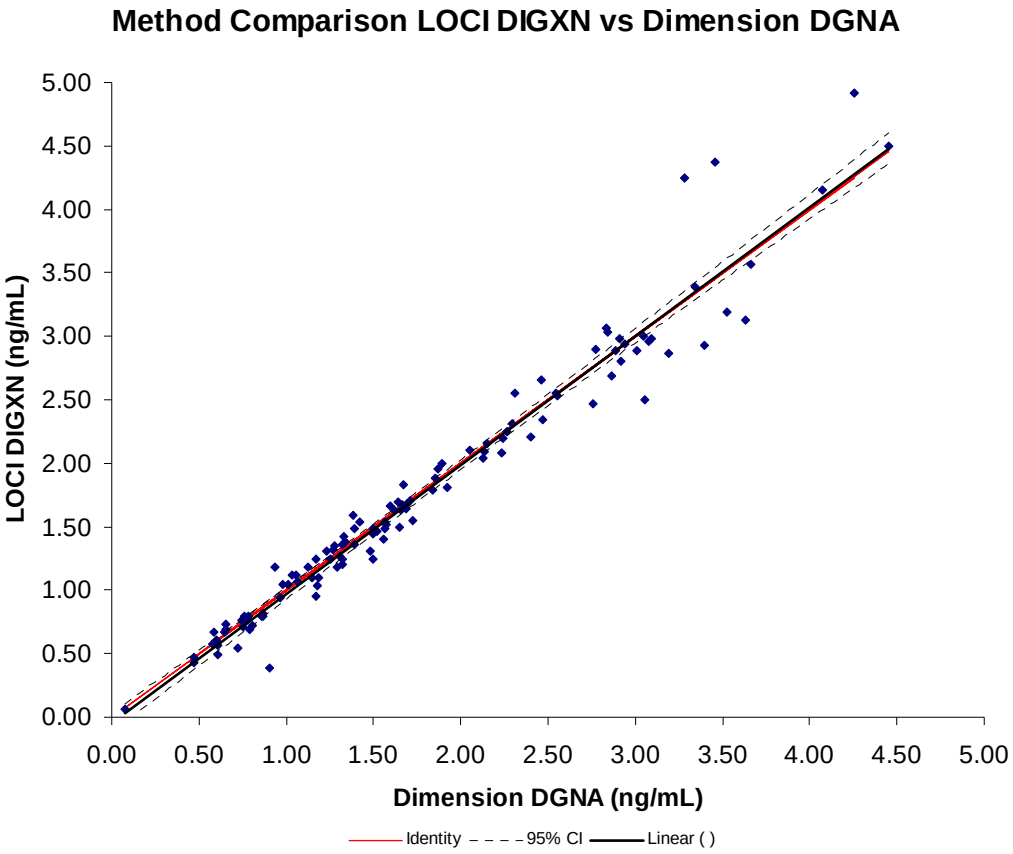
a. Method comparison with predicate device:

A split sample method comparison study between the Dimension® DGNA Digoxin Flex® reagent cartridge, (predicate) method and the Dimension Vista® LOCI DIGXN method was performed following CLSI Approved Guideline EP9-A2. De-identified, banked serum and lithium heparin plasma remnant samples within the assay range were selected from patients previously tested. No other selection criteria were applied.

The overall sample concentration range was 0.08 - 4.45 ng/mL. Regression statistics for combined serum and plasma samples (based on single measurements of each method) are:

Slope: 1.02 [0.98 to 1.06]
Intercept: -0.04 [-0.12 to 0.04]
R=0.98
Sy/x = 0.20 ng/mL

Similar results were obtained for both serum and plasma samples. The method comparison graph is shown below.



b. Matrix comparison:

Comparisons of matched patient serum and lithium heparin samples (n=85) were performed with samples containing with digoxin concentrations across the assay range. Results of linear regression are shown below:

Slope = 1.01

Intercept = 0.03 ng/mL

r = 0.997

Sy/x = 0.08 ng/mL

3. Clinical studies:

a. Clinical Sensitivity:

N/A. Not typically submitted for this type of assay.

b. Clinical specificity:

N/A. Not typically submitted for this assay type.

c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off**:**

   See expected values below.

5. Expected values/Reference range:

   The manufacturer includes the following in the package insert, with literature citations:

   The therapeutic range of 0.80 – 2.00 ng/mL [1.02 – 2.56 nmol/L] includes effective serum concentrations for a wide range of patient populations, although lower concentrations of 0.5 – 1.2 ng/mL [0.64 – 1.54 nmol/L] have been found to be more appropriate in certain populations such as chronic heart failure patients. Digoxin toxicity is commonly associated with serum levels > 2.0 ng/mL [2.6 nmol/L] but may occur with lower digoxin levels. Significant overlap of toxic and nontoxic values has been reported. Consequently, analysis of serum concentrations alone is not efficient for optimization of digoxin therapy. Additional factors such as age, thyroid condition, electrolyte balance, hepatic and renal functions, and other clinical symptoms must be considered. Each laboratory should determine the appropriateness of this range for the diagnostic evaluation of patient results.

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 substantial equivalence decision.