510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193397

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

ADVIA Centaur® Digoxin assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
KXT	Class II	21 CFR 862.3320 - Digoxin Test System	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

To add plasma sample type (EDTA and Lithium Heparin)

B Measurand:

Digoxin

C Type of Test:

Quantitative enzyme immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
For in vitro diagnostic use in the quantitative determination of digoxin in serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur XP systems. Measurements obtained by this device are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to ensure appropriate therapy.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:

The assay is to be used on the ADVIA Centaur® XP.

IV Device/System Characteristics:

A Device Description:

The ADVIA Centaur® Digoxin assay reagents are available in two configurations consisting of either one or five ReadyPack primary reagent packs and the ADVIA Centaur DIG Master Curve.

Each ReadyPack consists of the following:

- ADVIA Centaur DIG ReadyPack® primary reagent pack; Lite Reagent 2.5 mL/reagent pack monoclonal mouse anti-digoxin antibody (~26.4 ng/mL) labeled with acridinium ester in protein buffered saline with sodium azide (0.11%) and preservatives.
- ADVIA Centaur DIG ReadyPack primary reagent pack; Solid Phase Reagent 12.5 mL/reagent pack digitoxin (~2 ng/mL) covalently coupled to paramagnetic particles in protein buffered saline with sodium azide (0.11%) and preservatives.

B Principle of Operation:

The ADVIA Centaur Digoxin assay is a competitive immunoassay using digitoxin, which is covalently coupled to paramagnetic particles in the Solid Phase for a limited amount of acridinium ester-labeled monoclonal mouse anti-digoxin antibody in the Lite Reagent. Within the patient sample, the digoxin competes with the digitoxin, and an inverse relationship exist between the amount of digoxin present and the amount of relative light units detected by the system.

V Substantial Equivalence Information:

A Predicate Device Name(s):
ACS Digoxin Immunoassay

B Predicate 510(k) Number(s):
K931213

C Comparison with Predicate(s):

Device & Predicate Device(s):	K193397	K931213
Device Trade Name	ADVIA Centaur® Digoxin assay	ADVIA Centaur® Digoxin assay
General Device Characteristic Similarities		
Intended Use/Indications For Use	For in vitro diagnostic use in the quantitative determination of digoxin.	Same
Measurement	Quantitative	Same
Assay Principle	Competitive Immunoassay	Same
Technology	Direct chemiluminescent	Same
General Device Characteristic Differences		
Sample Type	Serum, lithium heparin and K2-EDTA plasma	Serum

VI Standards/Guidance Documents Referenced:

CLSI EP07: Interference Testing in Clinical Chemistry; Approved Guideline—Third Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Previously established in k932123.

2. Linearity:

   Previously established in k932123.

3. Analytical Specificity/Interference:

Testing of interferents was performed using the paired difference approach and was performed to simulate effect of partially filled blood collection plasma tube. Human K2-EDTA and lithium heparin pools, one at low and the other at high digoxin level for each matrix were used to titrate the anticoagulants. The nominal EDTA and Heparin concentrations are 1.8 mg/mL and 15.0 U/mL in blood collection tubes respectively. EDTA and Heparin were spiked 3 times and 5 times the additive concentration for testing with the candidate device. Each of these sample matrices had an aliquot as a control (spiked with deionized water) and an aliquot spiked with interferent. Testing was performed on one ADVIA Centaur® system with one reagent lot in 10 replicates. The observed interference effect, Dobs, was computed as the difference between the means of the test and control samples.

Dobs = Interference = (test sample mean – control sample mean)

To report the level of interferent for a quantitative assay as percent (%) bias, the following calculation was used: % Bias = [100* Dobs] / [control sample mean]

The sponsor defined significant interference as a bias > ±10%. Results are summarized below:

Potential interferent	Highest concentration tested that showed no interference
K2-EDTA	9.0 mg/mL
Lithium heparin	75 U/mL

The sponsor also conducted interference testing to evaluate the effect of endogenous substances - Spironolactone, Canrenone and Potassium Canrenoate that may be present in specimens. Testing consisted of human serum pools at two levels of digoxin used to titrate the testing compounds in the paired difference approach, by dividing the two serum pools into aliquots and spiked with the possible interferents. The control samples without the interferent were spiked with the solvent. The digoxin concentration of the spiked samples was compared to the digoxin concentration determined for the control samples. Testing was performed on one ADVIA Centaur® XP system with one reagent lot in 8 replicates per sample. The observed interference effect, Dobs, was computed as the difference between the means of the test and control samples. Results are summarized below:

Interferent	Highest concentration tested that showed no interference
Canrenone	1000 ng/mL
Spironolactone	1000 ng/mL
Potassium Canrenoate	1000 ng/mL

4. Assay Reportable Range:

The reportable range of the assay is from 0.1 to 5.0 ng/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   The ADVIA Centaur Digoxin assay is traceable to an internal standard manufactured using U.S.P. (United States Pharmacopeia) material. Assigned values for calibrators are traceable to this standardization."

   The sponsor has provided data to support the following sample stability claims:

   Do not use samples that have been stored at room temperature for longer than 8 hours.
   Tightly cap and refrigerate specimens at 2–8°C if the assay is not completed within 8 hours.
   Freeze samples at or below -20°C if the sample is not assayed within 48 hours.
   Freeze samples only once and mix thoroughly after thawing.

6. Detection Limit:

   Previously established in k932123.

7. Assay Cut-Off:
   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Previously established in k932123.

2. Matrix Comparison:

   The sponsor provided an additional matrix comparison study as follows. Human matched serum, K2-EDTA plasma and lithium heparin plasma samples were tested in singlet on one ADVIA Centaur® XP system using two reagent lots. Results are summarized below.

Reference Matrix (x)	Test Matrix (y)	N	r	Regression Equation	Sample Range (ng/mL)
Serum	EDTA plasma	51	0.996	y= 1.02 x - 0.02	0.14 – 4.81
Serum	Lithium heparin plasma	50	0.990	y= 1.06 x - 0.03	0.14 – 4.88

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The sponsor included the following information and references in the labeling:

A therapeutic range of 0.8 to 2.0 ng/mL (1.024 to 2.56 nmol/L) has been previously reported for digoxin.[1,2]
It is important to point out that the distinction between adequate digitalization and toxicity in patients cannot be made on the basis of digoxin concentration alone. Findings must be interpreted with a knowledge of this limitation.
As with all therapeutic drug assays, each laboratory should determine the appropriateness of this range for the diagnostic evaluation of patient results.[3]

References:

1. Taggart AJ, McDevitt DG. Digitalis: Its place in modern therapy. Drugs. 1980;20:398–404.

2. Graves SW, Valdes R, Brown BA, et al. Endogenous digoxin-immunoreactive substance in human pregnancies. J Clin Endocrin Metab. 1984;58:748–51.

3. Clinical and Laboratory Standards Institute (formerly NCCLS). Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition. Wayne, PA: Clinical and Laboratory Standards Institute; 2008. CLSI Document C28-A3.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.