510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

I Background Information:

A 510(k) Number

K200215

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

ADVIA Centaur CEA Assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DHX	Class II	21 CFR 866.6010 - Tumor-Associated Antigen Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared device: addition of Li-Heparin and K2-EDTA plasma matrices.

B Measurand:

Carcinoembryonic antigen 125 (CEA)

C Type of Test:

Quantitative, Chemiluminescent

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

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 measurement of carcinoembryonic antigen (CEA) in serum and plasma (EDTA and lithium heparin) to aid in the management of cancer patients in whom changing concentrations of CEA are observed using the ADVIA Centaur XP and ADVIA Centaur XPT systems.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

For use on the ADVIA Centaur XP and ADVIA Centaur XPT

IV Device/System Characteristics:

A Device Description:

The ADVIA Centaur CEA Assay kit contains the following:

- ReadyPack primary reagent packs for 100 or 500 tests
- ADVIA Centaur CEA Master Curve card

The ReadyPack for ADVIA Centaur CEA consists of the following:

- CEA Lite Reagent: 5.0 mL polyclonal rabbit anti-CEA antibody (~400 ng/mL) labeled with acridinium ester in phosphate buffered saline with protein stabilizers, sodium azide (0.12%), and preservatives.
- CEA Solid Phase Reagent: 25.0 mL monoclonal mouse anti-CEA antibody (~120 µg/mL) covalently coupled to paramagnetic particles in phosphate buffered saline with protein stabilizers, sodium azide (0.11%), and preservatives.
- CEA diluent: 5.0 mL bicine buffer, gelatin, and BSA with preservatives and sodium azide (0.1%)

Materials Required but not provided:

- ADVIA Centaur Calibrator D

Optional Reagents:

- ADVIA Centaur CEA Master Curve Material
- ADVIA Centaur CEA Diluent

B Principle of Operation:

The ADVlA Centaur CEA Assay is a fully automated, single-wash sandwich immunoassay using direct, chemiluminescent technology. The Lite Reagent is composed of the polyclonal rabbit anti-CEA antibody labeled with acridinium ester. The Solid Phase Reagent is composed of monoclonal mouse anti-CEA antibody covalently coupled to paramagnetic particles. The sample is incubated with the Lite Reagent and Solid Phase Reagent for 7.5 minutes at 37 °C to allow formed immune complexes to be captured by the particles. After incubation, the particles are washed before addition of the Acid Reagent and Base Reagent to initiate the chemiluminescent reaction. The measured chemiluminescence is directly proportional to the quantity of CEA antigen in the sample.

V Substantial Equivalence Information:

A Predicate Device Name(s):

ACS:Centaur CEA

B Predicate 510(k) Number(s):

K981478

C Comparison with Predicate(s):

Device & Predicate Device(s):	K200199 Device	K981478 Predicate
Device Trade Name	ADVIA Centaur CEA Assay	ACS:Centaur CEA
General Device Characteristic Similarities		
Intended Use/ Indications for Use	For in vitro diagnostic use in the quantitative measurement of carcinoembryonic antigen (CEA) in serum and plasma (EDTA and lithium heparin) to aid in the management of cancer patients in whom changing concentrations of CEA are observed using the ADVIA Centaur XP and ADVIA Centaur XPT systems.	For in vitro diagnostic use in the quantitative measurement of carcinoembryonic antigen (CEA) in serum to aid in the management of cancer patients in whom changing concentrations of CEA are observed using the ADVIA Centaur®, ADVIA Centaur XP, and ADVIA Centaur XPT systems.
Operating Principle	Single wash sandwich immunoassay	Same
Assay Technology	Direct chemiluminescent	Same
Measurement	Quantitative	Same
Sample Volume	50 µL	Same
Reagent Volume	50 µL of Lite Reagent and 250 µL	Same

	of Solid Phase	
Detection Antibody	Polyclonal rabbit anti-CEA antibody labeled with acridinium ester	Same
Capture Antibody	Monoclonal mouse anti-CEA antibody covalently coupled to paramagnetic particles	Same
Traceability	The ADVIA Centaur CEA assay is traceable to an internal standard manufactured using highly purified material. Assigned values for calibrators are traceable to this standardization	Same
Calibrators	ADVIA Centaur Calibrator D/ Two levels	Same
Calibration	Two-point	Same
Controls	Commercial Controls /Two levels	Same
General Device Characteristic Differences		
Sample Type	Serum, plasma (EDTA and lithium heparin)	Serum
Detection Capability	LoB: 0.5 ng/mL LoD: 1.0 ng/mL LoQ: 2.0 ng/mL	Analytical Sensitivity: 0.5 ng/mL
Assay Range	2.0–100 ng/mL	0.5–100 ng/mL

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition

CLSI EP06-A, Evaluation of Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP07, 3rd Edition, Interference Testing in Clinical Chemistry

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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The precision and reproducibility of the ADVIA Centaur CEA Assay were demonstrated in K981478.

2. Linearity:

The linearity of the ADVIA Centaur CEA Assay was demonstrated in K981478.

3. Analytical Specificity/Interference:

The analytical specificity was demonstrated in K981478. Interference was evaluated with hemoglobin, triglycerides, bilirubin and chemotherapeutic agents. The potential interference of NCA (normal cross-reacting antigen) and NCA2 was also evaluated.

To evaluate the performance of the ADVIA Centaur CEA Assay in samples collected with K2-EDTA and lithium heparin tubes, one sample at low level and one at high level of CEA for each matrix were used to titrate the EDTA and heparin anticoagulants. The nominal K2-EDTA and lithium heparin concentrations are 1.8 mg/mL and 15.0 U/mL in blood collection tubes, respectively. Both K2-EDTA and lithium heparin samples were spiked at three times and five times the nominal additive concentration for testing. Testing was performed in three replicates per sample on one ADVIA Centaur XP instrument using one lot of reagent. The recovery was calculated as the difference between the means of the test samples spiked with the interferent and control samples spiked with the same volume of the interferent vehicle. Results summarized in the table below show that no significant assay interference was demonstrated with K2-EDTA and lithium heparin at the indicated test concentrations.

Interferent	**Interferent Test concentration**	**Low level CEA sample**		**High level CEA sample**	
		Mean (ng/mL)	Recovery (%)	Mean (ng/mL)	Recovery (%)
K2-EDTA	5.4 mg/mL	5.55	96.2	58.34	104.9
	9.0 mg/mL	5.76	99.7	58.20	104.6
Lithium heparin	45 U/mL	5.82	99.8	62.17	101.5
	75 U/mL	5.80	99.4	61.77	100.1

4. Assay Reportable Range:

The claimed measuring range is from 2.0 ng/mL to 100 ng/mL.

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

The traceability and reagent stability were established in K981478.

6. Detection Limit:

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation for the ADVIA Centaur CEA Assay were determined in accordance with the CLSI guideline EP17-A2.

The LoB was determined using two lots of reagents and one ADVIA Centaur XP instrument. Five analyte-free human serum pools were tested in five replicates per run, two runs per day for five days, to obtain a total of 250 replicates per lot. The LoB was estimated as the 95th percentile of the measurements and determined to be 0.15 ng/mL and 0.36 ng/mL for the two lots of reagents. The claimed LoB is 0.5 ng/mL.

The LoD was determined using 10 serum pools with low analyte levels on one ADVIA Centaur XP instrument using two lots of reagents. All samples were tested in five replicates per sample for ten runs over a period of five days yielding a total of 500 replicates per reagent lot. The LoD was determined as 0.46 ng/mL and 0.48 ng/mL for the two lots of reagents. The claimed LoD is 1.0 ng/mL.

The LoQ was determined using 10 serum pools with low analyte levels on one ADVIA Centaur XP instrument using two lots of reagents. All samples were tested in five replicates per sample for ten runs over a period of five days yielding a total of 500 replicates per reagent lot. The LoQ defined as the mean value of the sample which fulfills the specification for the total within-laboratory imprecision ≤ 20% CV is 0.29 ng/mL and 0.43 ng/mL for the two lots of reagents. The claimed LoQ is 2.0 ng/mL which is the lower limit of the measuring range claimed for the assay.

7. Assay Cut-Off:

The assay cut-off was demonstrated in K981478.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The method comparison with predicate device was presented in K981478. Results from this study were re-analyzed to determine the relationship of the ADVIA Centaur CEA assay to the ACS:180 CEA assay. A total of 284 samples with CEA concentrations ranging from 0.5 to 78.5 ng/mL were tested. Because the lower limit of the measuring range was raised from 0.5 ng/mL to 2.0 ng/mL, 83 samples with CEA concentrations below 2.0 ng/mL were removed from the analysis. A Deming regression analysis was performed for the remaining 201 samples and the results are summarized in the following table:

Comparison	N	Sample Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient (r)
ADVIA Centaur CEA vs. ACS:180 CEA	201	2.0 – 78.9	0.97 (0.96 – 0.98)	0.11 (-0.26 – 0.48)	1.00
N = Number of samples tested					

2. Matrix Comparison:

To demonstrate that Li-Heparin plasma and K2-EDTA plasma samples yield results comparable with serum samples by the ADVIA Centaur CEA Assay, a study was performed by using 64 serum/K2-EDTA plasma paired samples (59 native samples and five pooled

samples) and 46 serum/Li-heparin plasma paired samples (41 native samples and five pooled samples). The pooled sample pairs were prepared by mixing high CEA and low CEA native human matched pairs. Paired samples were each tested in singleton using five reagent lots on three ADVIA Centaur XP instruments. The Deming regression analysis was performed, and the results are summarized in the following table:

Comparison	N	Sample Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient (r)
K2-EDTA plasma vs. serum	64	2.1 – 97.1	0.95 (0.91 – 0.99)	0.20 (-0.45 – 0.85)	1.00
Lithium Heparin plasma vs. serum	46	2.1 – 97.1	0.99 (0.95 – 1.04)	0.19 (-0.27 – 0.64)	1.00
N = Number of samples tested					

The data support the addition of K2-EDTA plasma and Li-heparin plasma sample types to the ADVIA Centaur CEA Assay.

C Clinical Studies:

Clinical Sensitivity and Specificity:

The clinical sensitivity and specificity of the assay was demonstrated in K981478.

D Clinical Cut-Off:

The clinical cut-off was demonstrated in K981478.

E Expected Values/Reference Range:

The expected values were established in K981478.

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.