510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

I Background Information:

A 510(k) Number

K200199

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

ADVIA Centaur CA 125 II Assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LTK	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 previous cleared device: addition of Li-Heparin and K2-EDTA plasma matrices.

B Measurand:

Cancer Antigen 125 (CA 125)

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, serial determination of CA 125 in human serum and plasma (EDTA and lithium heparin) and to aid in the management of patients with ovarian carcinoma using the ADVIA Centaur XP and ADVIA Centaur XPT systems. The test is intended for use as an aid in monitoring patients previously treated for ovarian cancer. Serial testing for CA 125 in the serum and plasma of patients who are clinically free of disease should be used in conjunction with other clinical methods used for the early detection of cancer recurrence. The test is also intended for use as an aid in the management of ovarian cancer patients with metastatic disease by monitoring the progression or regression of disease in response to treatment. It is recommended that the ADVIA Centaur CA 125II assay be used under the order of a physician trained and experienced in the management of gynecological cancers. This assay is not intended for screening or diagnosis of ovarian cancer or for use on any other system.

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 CA 125II Assay kit contains the following:
- ReadyPack, primary reagent packs for 100 or 500 tests
- ADVIA Centaur CA 125II Master Curve card

The ReadyPack for ADVIA Centaur CA 125II consists of the following:
- CA 125II Lite Reagent: 10.0 mL monoclonal mouse anti-M11 antibody labeled with acridinium ester and monoclonal mouse anti-OC 125 labeled with fluorescein in phosphate buffer with bovine serum albumin (BSA) and preservatives
- CA 125II Solid Phase Reagent: 25.0 mL monoclonal mouse anti-fluorescein antibody coupled to paramagnetic particles in phosphate buffer with BSA and preservatives

Materials Required but not provided:
- ADVIA Centaur CA 125II Calibrator

Optional Reagents

- ADVIA Centaur CA125II Master Curve Material
- ADVIA Centaur Multi-Diluent 1

B Principle of Operation:

The ADVlA Centaur CA 125II Assay is a fully automated, single-wash sandwich immunoassay using direct, chemiluminescent technology, which uses two monoclonal mouse antibodies specific for CA 125. The first antibody in the Lite Reagent is composed of the monoclonal mouse antibody toward the CA125 M11 antigenic domain and is labeled with acridinium ester. The second antibody is directed toward the CA125 OC 125 antigenic domain and is labeled with fluorescein. The immunocomplex formed with CA 125 is captured with monoclonal mouse anti-fluorescein antibody coupled to paramagnetic particles in the Solid Phase Reagent. The sample is incubated with the Lite Reagent for 7.5 minutes at 37 °C to allow immune complexes to form. The particles in the Solid Phase Reagent are then added and incubated for an additional 40 minutes at 37 °C to capture the immune complexes. After incubation, the particles are washed before addition of the Acid Reagent and Base Reagent to initiate the chemiluminescent reaction. The amount of relative light units (RLUs) detected by the system is directly proportional to the quantity of CA 125 antigen present in the patient sample.

V Substantial Equivalence Information:

A Predicate Device Name(s):

CA 125 Assay for the ADVIA Centaur System

B Predicate 510(k) Number(s):

K020828

C Comparison with Predicate(s):

Device & Predicate Device(s):	K200199 Device	K020828 Predicate
Device Trade Name	ADVIA Centaur CA 125II Assay	ADVIA Centaur CA 125II Assay
General Device Characteristic Similarities		
Intended Use/ Indications for Use	For *in vitro* diagnostic use in the quantitative, serial determination of CA 125 in human serum and plasma (EDTA and lithium heparin) and to aid in the management of patients with ovarian carcinoma using the ADVIA Centaur XP and ADVIA Centaur XPT systems. The test is intended for use as an aid in	For *in vitro* diagnostic use in the quantitative, serial determination of CA 125 in human serum and to aid in the management of patients with ovarian carcinoma using the ADVIA Centaur, ADVIA Centaur XP, and ADVIA Centaur XPT systems. The test is intended for use as an aid in monitoring patients previously

	monitoring patients previously treated for ovarian cancer. Serial testing for CA 125 in the serum and plasma of patients who are clinically free of disease should be used in conjunction with other clinical methods used for the early detection of cancer recurrence. The test is also intended for use as an aid in the management of ovarian cancer patients with metastatic disease by monitoring the progression or regression of disease in response to treatment. It is recommended that the ADVIA Centaur CA 125 II assay be used under the order of a physician trained and experienced in the management of gynecological cancers. This assay is not intended for screening or diagnosis of ovarian cancer or for use on any other system.	treated for ovarian cancer. Serial testing for CA 125 in the serum of patients who are clinically free of disease should be used in conjunction with other clinical methods used for the early detection of cancer recurrence. The test is also intended for use as an aid in the management of ovarian cancer patients with metastatic disease by monitoring the progression or regression of disease in response to treatment. It is recommended that the ADVIA Centaur CA 125 II assay be used under the order of a physician trained and experienced in the management of gynecological cancers. This assay is not intended for screening or diagnosis of ovarian cancer or for use on any other system.
Operating Principle	Single wash sandwich immunoassay	Same
Assay Technology	Direct chemiluminescent	Same
Measurement	Quantitative	Same
Sample Volume	50 µL	Same
Capture Antibody	Monoclonal mouse anti-fluorescein antibody coupled to paramagnetic particles	Same
Detection Antibody	Monoclonal mouse anti-M11 antibody labeled with acridinium ester and monoclonal mouse anti-OC 125 labeled with fluorescein	Same
Calibrators	ADVIA Centaur CA 125II Calibrator (Two levels)	Same
Controls	Commercial Controls/ (Two levels)	Same
General Device Characteristic Differences		
Sample Type	Serum, plasma (EDTA and lithium heparin)	Serum
Detection Capability	LoB: 2.0 U/mL LoD: 3.0 U/mL LoQ: 3.0 U/mL	Analytical Sensitivity: 2 U/mL
Assay Range	3.0–600 U/mL	2–600 U/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 assay were demonstrated in K020828.

2. Linearity:

   The linearity of the assay was demonstrated in K020828.

3. Analytical Specificity/Interference:

   The analytical specificity was demonstrated in K020828. Interference was evaluated with hemoglobin, lipids, bilirubin, total protein, chemotherapeutic agents, therapeutic drugs and tumor marker antigens.

   To evaluate the performance of the ADVIA Centaur CA 125 II assay in samples collected with K2-EDTA and lithium heparin tubes, one sample at low and one at high level of CA125 for each matrix were used to titrate the EDTA and heparin anticoagulants in order to simulate the effect of partially filled blood collection plasma tube. 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 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. Results are summarized in the table below:

Interferent	Interferent test concentration	CA125 low level sample		CA 125 high level sample	
		Mean (IU/mL)	Recovery (%)	Mean (IU/mL)	Recovery (%)
K2-EDTA	5.4 mg/mL	41.1	104.0	532.1	101.1
	9.0 mg/mL	41.0	103.7	533.5	101.3
Lithium heparin	45 U/mL	42.6	100.6	478.7	101.5
	75 U/mL	43.7	103.2	467.2	99.1

4. Assay Reportable Range:

   The claimed measuring range is from 3.0 U/mL to 600 U/mL.

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

   The traceability and reagent stability were established in K020828.

6. Detection Limit:

   The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) for the ADVIA Centaur CA 125II 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 samples 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 0.18 U/mL and 0.61 U/mL for the two lots of reagents. The claimed LoB is 2.0 U/mL.

   The LoD was determined using 15 serum pools with low analyte levels (0.09−16.67 U/mL). Each sample was tested in five replicates per run, two runs per day, for five days on one ADVIA Centaur XP instrument using two lots of reagents to obtain a total of 750 replicates per lot for all 15 samples. The LoD was determined as 0.73 U/mL and 0.67 U/mL for the two lots of reagents. The claimed LoD is 3.0 U/mL.

   The LoQ was determined using the same set of 15 serum pools with low analyte levels. Each sample was tested in five replicates per run, two runs per day, for five days on one ADVIA Centaur XP instrument using two lots of reagents to obtain a total of 750 replicates per lot for all 15 samples. The LoQ defined as the mean value of the sample which fulfills the specification for the total within-laboratory imprecision ≤ 20% CV is 0.18 U/mL and 0.13 U/mL for the two lots of reagents. The claimed LoQ is 3.0 U/mL which is the lower limit of the measuring range claimed for the assay.

7. Assay Cut-Off:

   The cutoff of the assay was demonstrated in K020828.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The method comparison with the predicate device was presented in K020828. Results from this study were re-analyzed to determine the relationship of the ADVIA Centaur CA 125II assay to the Bayer Immuno-1 CA 125II assay. A total of 227 serum samples with CA 125 concentrations ranging from 2.3 to 466.6 U/mL were tested. Because the lower limit of the measuring range was raised from 2.0 U/mL to 3.0 U/mL, three samples with CA 125 concentrations below 3.0 U/mL were excluded from the analysis. A Deming regression analysis was performed for the remaining 224 samples and the results are summarized in the following table:

Comparison	N	Sample Range (U/mL)	Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient (r)
ADVIA Centaur CA 125II vs. Immuno-1 CA 125II	224	3.1–466.6	1.03 (1.01–1.04)	1.15 (-0.81–3.11)	0.99
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 CA 125II assay, a study was performed by using 162 serum/K2-EDTA plasma paired samples (153 native and 9 pooled samples) and 135 serum/Li-heparin plasma paired samples (112 native and 8 pooled samples). Paired samples were each tested in singleton on ADVIA Centaur XP system. The Deming regression analysis was performed, and the results are summarized in the following table:

Comparison	N	Sample Range (U/mL)	Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient (r)
K2-EDTA plasma vs. serum	162	3.0–572.7	0.95 (0.92–0.98)	-0.4 (-1.50–0.72)	1.00
Lithium Heparin plasma vs. serum	119	3.1–572.7	1.02 (0.98–1.07)	-0.2 (-1.55–1.32)	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 CA 125II assay.

C Clinical Studies:

1. Clinical Sensitivity and Specificity:

The clinical sensitivity and specificity of the assay was demonstrated in K020828.

D Clinical Cut-Off:

The clinical cutoff of the assay was demonstrated in K020828.

E Expected Values/Reference Range:

The expected values were established in K020828.

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.