510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K240479

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

Access OV Monitor

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 the previously cleared device – change of substrate, sample volume and updated analytical measuring interval of the assay on the DxI 9000 Immunoassay Analyzer

B Measurand:

Cancer Antigen (CA) 125

C Type of Test:

Quantitative, Chemiluminescent immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Access OV Monitor assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of CA 125 antigen levels in human serum and plasma using the Access Immunoassay Systems. This device is indicated for use in the measurement of CA 125 antigen to aid in the management of ovarian cancer patients. Serial testing for patient CA 125 antigen concentrations should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The Instruction for Use of the device contains the following warnings:

The concentration of CA 125 antigen in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the CA 125 antigen assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining CA 125 antigen values is changed, additional sequential testing should be carried out to confirm baseline values.

D Special Instrument Requirements:

DxI 9000 Access Immunoassay Analyzer (K221225)

IV Device/System Characteristics:

A Device Description:

Each Access OV Monitor Reagent Pack contains two reagent packs (50 tests/pack). Each pack contains the following:

- Paramagnetic particles, coated with goat anti-biotin antibodies, biotinylated anti CA 125 antigen mouse monoclonal antibodies, bovine serum albumin, < 0.1% sodium azide, and 0.1% ProClin 300.
- Mouse monoclonal anti-CA 125 antigen-alkaline phosphatase (bovine) conjugate, bovine serum albumin, < 0.1% sodium azide, and 0.1% ProClin 300.
- Buffered protein solution (bovine, goat, mouse), < 0.1% sodium azide and 0.1% ProClin 300.

Materials needed but not supplied with reagent kit:

- Access OV Monitor Calibrators: at approximately 0, 25, 100, 500, 2,000 and 5,000 U/mL
- Quality Control (QC) materials: commercial control material
- Substrate: Lumi-Phos PRO

- UniCel DxI Wash Buffer II
- Access Sample Diluent A (optional)

The modification of the Access OV Monitor includes:
(a) a new substrate replacement (Lumi-Phos PRO)
(b) run on DxI 9000 Access Immunoassay Analyzer with updated analytical measuring interval of 2.0 – 5,000 U/mL

B Principle of Operation:

The Access OV Monitor assay is a two-site immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel along with mouse monoclonal anti-CA 125 antigen alkaline phosphatase conjugate and paramagnetic particles coated with a second mouse monoclonal anti-CA 125 antigen antibody. The CA 125 antigen in the sample binds to the immobilized monoclonal anti-CA 125 antigen on the solid phase, while the conjugate antibody reacts with a different antigenic site on the CA 125 antigen molecule. After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access OV Monitor Immunoenzymetric Assay

B Predicate 510(k) Number(s):

K023597

C Comparison with Predicate(s):

Device & Predicate Device(s):	K240479 Candidate Device	K023597 Predicate
Device Trade Name	Access OV Monitor	Same
General Device Characteristic Similarities		
Intended Use/ Indications For Use	The Access OV Monitor assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of CA 125 antigen levels in human serum and plasma using the Access Immunoassay Systems. This device is indicated for use in the measurement of CA 125 antigen to aid in the management of ovarian cancer patients. Serial testing	Same

	for patient CA 125 antigen concentrations should be used in conjunction with other clinical methods used for monitoring ovarian cancer.	
Measurand	CA 125 antigen	Same
Sample Type	Serum and Plasma (heparin)	Same
Assay Technology	Chemiluminescent	Same
Format	Sandwich Immunoassay	Same
Measurement	Quantitative	Same
Antibody	Monoclonal (mouse) anti-CA 125 antibodies	Same
Calibrators	Utilizes a stored calibration curve	Same
Reagent Stability	28 days after opening	Same
Method	Automated	Same
General Device Characteristic Differences		
Instrument	DxI 9000 Access Immunoassay Analyzer	Access Immunoassay system
Substrate	Lumi-Phos PRO substrate	Access Substrate
Measuring Range	2.0 – 5,000 U/mL	0.5 – 5000 U/mL
Sample Volume	30 µL	25 µL

VI Standards/Guidance Documents Referenced:

The following Clinical and Laboratory Standards Institute (CLSI) guidelines were used:

- CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition
- CLSI EP06 2nd Edition, Evaluation of Linearity of Quantitative, Measurement Procedures
- CLSI EP09c 3rd Edition, Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition
- CLSI EP34 1st Edition, Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision testing was performed in accordance with CLSI guideline EP05-A3.

a) Within-Laboratory Precision

The studies were performed at a single site using one lot of the modified Access OV Monitor reagent on one DxI 9000 Access Immunoassay Analyzer. Five levels of human serum samples were run in a minimum of three replicates per run, two runs daily over the course of 20 days, resulting a minimum of 120 datapoints for each sample. The data were analyzed for repeatability (within-run), between-run, between-day, and within-laboratory precision. The mean (U/mL), standard deviation (SD) (U/mL) and percent coefficient of variation (%CV) are summarized in table below.

Sample	N	Mean (U/mL)	Within-Run (Repeatability)		Between-Run		Between-Day		Within-Laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	120	5.5	0.1	1.7	0.1	1.6	0.2	3.4	0.2	4.1
2	120	54	1.6	2.9	0.0	0.0	1.2	2.2	2.0	3.6
3	120	89	1.5	1.6	1.7	1.8	1.2	1.3	2.5	2.8
4	120	524	9.4	1.8	5.8	1.1	8.7	1.7	14.0	2.7
5	120	1578	30.0	1.9	17.8	1.1	20.8	1.3	40.6	2.6
6	120	2,837	94.9	3.3	23.3	0.8	131.2	4.6	163.7	5.8
7	120	3,632	101.6	2.8	52.9	1.5	162.4	4.5	198.7	5.5
8	120	4,489	128.1	2.9	28.4	0.6	239.4	5.3	273.0	6.1

b) Lot-to-Lot Precision

The lot-to-lot precision of Lumi-Phos PRO Substrate was assessed in K223921.

The lot-to-lot precision of the modified Access OV Monitor reagent was performed at a single site using three reagent lots with one Access OV Monitor Calibrator lot, and on three DxI 9000 Analyzers. Five levels of serum samples were run in five replicates per run, one run per day over the course of five days, resulting a total of 75 datapoints for each sample on each instrument. The data were analyzed for repeatability (within-run), between-day, between-reagent lot, and total precision. The mean (U/mL), standard deviation (SD) (U/mL) and percent coefficient of variation (%CV) on one representative instrument are summarized in table below:

Sample	N	Mean (U/mL)	Within-Run (Repeatability)		Between-Day		Between-Reagent Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	75	5.4	0.1	2.3	0.1	1.1	0.1	1.3	0.2	2.9
2	75	38	0.8	2.2	0.8	2.0	0.0	0.0	1.1	3.0
3	75	88	1.5	1.7	2.0	2.3	0.9	1.1	2.7	3.1
4	75	2845	49.8	1.8	49.6	1.7	15.6	0.5	72	2.5
5	75	3761	72.3	1.9	87.4	2.3	15.8	0.4	114.5	3.0

c) Instrument-to-Instrument Reproducibility

The study was performed using three DxI 9000 Access Immunoassay Analyzers. Five levels of serum samples were used across three modified Access OV Monitor reagent lots and one calibrator lot on each instrument run in five replicates per run, one run per day over the course of five days, resulting a total of 75 datapoints for each sample on each instrument. The data were analyzed for within-run, between-day, between-instrument, and reproducibility. The mean (U/mL), standard deviation (SD) (U/mL) and percent coefficient of variation (%CV) using one representative reagent lot are summarized in table below:

Sample	N	Mean (U/mL)	Repeatability (Within-run)		Between-Day		Between-Instrument		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	75	5.4	0.1	2.3	0.0	0.0	0.1	1.2	0.1	2.6
2	75	39	0.9	2.3	0.3	0.7	0.4	1.1	1.0	2.7
3	75	88	1.3	1.5	1.7	1.9	0.2	0.3	2.2	2.4
4	75	2,845	57.0	2.0	40.4	1.4	22.1	0.8	73.3	2.6
5	75	3,754	92.6	2.5	72.0	1.9	48.4	1.3	126.9	3.4

2. Linearity:

a) Linearity studies:

Linearity of the modified Access OV Monitor was performed in accordance with CLSI guideline EP06 2nd Edition. Two series of High samples were prepared by pooling human serum samples to achieve CA 125 concentrations of 360 U/mL (Sample-1) and 6,162 U/mL (Sample-2). Low sample was obtained from a single human serum sample that was specifically stripped of CA 125 antigen using paramagnetic particles to achieve a concentration below the low end of the AMI of the assay. The low sample in the two series was run in replicates of eight, and all other dilution levels were run in replicates of four, and the 'measured value' (mean CA 125 U/mL) was compared to its predicted value for deviation percentage using a weighted linear regression analysis. This deviation was then compared to the allowable deviation from linearity (ADL). The results are summarized in table below.

Sample	Range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R^2	% Deviation**
1	0.5 – 362	0.977 (0.968, 0.985)	-0.004 (-0.104, 0.096)	0.999	-3% – 3%
2	0.5 – 6,162	1.02 (1.010, 1.030)	-0.01 (-0.070, 0.050)	0.999	-2% – 5%
1 & 2*	0.5 – 6,162	1.00 (0.990, 1.00)	-0.01 (-0.080, 0.060)	1.000	-5% – 7%

* Combined from Sample 1 and 2

** % Deviation from Linearity for concentrations > 15 U/mL

The data support the linearity interval from 0.5 to 6,162 U/mL with the deviations from linearity within ±10%. The study results support the linearity of the claimed analytical measuring interval (AMI): 2.0 – 5,000 U/mL.

b) *Extended Measuring Interval (Auto Dilution):*

Extended measuring range study was conducted in accordance with CLSI guideline EP34, 1st Edition. A total of five individual human serum samples spiked with antigen to achieve doses within the extended measuring interval (EMI) of the assay concentrations between 8,000 U/mL and 100,000 U/mL. Two operators each prepared two independent 1:20 manual dilutions for each sample. Manual dilutions and dilutions performed by two DxI 9000 Access Immunoassay Analyzers were done with one Access OV Monitor reagent lot. Recovery results for dilution factor at 1:20 for samples with concentrations between 8,015 U/mL up to 83,361 U/mL are between 94% and 99%. These results showed that the dilution at 1:20 performed by the DxI 9000 Access Immunoassay Analyzer are consistent with manual dilutions.

3. Analytical Specificity/Interference:

a) *Endogenous/Exogenous Substance Interference*

Refer to K023597

b) *Carryover*

Carryover was established in K221225.

4. Assay Reportable Range:

The reportable range is the same as the claimed analytical measuring interval (AMI): 2.0 – 5,000 U/mL. The device allows auto-dilution of samples—the extended measuring interval (EMI) 'upper limit of quantitation' (ULOQ to the maximum dilution concentration) is 100,000 U/mL.

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

a) *Traceability:*

The traceability was established in K023597.

b) *Stability:*

The Access OV Monitor Reagent kit and the Lumi-Phos PRO substrate are packaged separately. Access OV Monitor Reagent kit stability was established in K023597. The proposed change is to replace substrate (Lumi-Phos 530) of the modified Access OV Monitor with a new substrate (Lumi-Phos PRO). The shelf-life claims and on-board stability claims of Lumi-Phos PRO substrate were established in K221225.

6. Detection Capability:

CLSI guideline EP17-A2 was followed to determine the Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) for the modified Access OV Monitor on DxI 9000 Access Immunoassay Analyzer.

a) LoB:

Five blank samples (individual native serum samples from which CA 125 was specifically depleted) were tested in five replicates per run, one run per day over three days using two modified Access OV Monitor reagent lots (N = 75 replicates for each lot) on two DxI 9000 Access Immunoassay Analyzers. The LoB for each reagent lot was calculated using the non-parametric approach and the maximum observed LoB is taken as the reported value for the measurement procedure. LoB determined using the 95% non-parametric percentile of the replicates for each of the two reagent lots was 0.2 U/mL. The claimed LoB for the modified Access OV Monitor on DxI 9000 Access Immunoassay Analyzer is 0.5 U/mL.

b) LoD:

Seven serum samples containing low levels of CA 125 were run in eight to nine replicates per run, one run per day over five days using three modified Access OV Monitor reagent lots (N = minimum 280 replicates for each lot) on two DxI 9000 Access Immunoassay Analyzers. The LoD was determined by fitting the precision profile model between within-laboratory SD and concentration. LoD calculated from LoB + "SD multiplied by the 95th percentile of the standard normal distribution" resulted in 0.3 U/mL for each reagent lot. The claimed LoD for the modified Access OV Monitor on DxI 9000 Access Immunoassay Analyzer is 0.7 U/mL.

c) LoQ:

A minimum of 13 serum samples containing low levels of CA 125 were run in nine replicates of per run, one run per day over five days using three modified Access OV Monitor reagent lots (N=minimum 585 replicates for each lot) on three DxI 9000 Access Immunoassay Analyzers. A variance components model was used to estimate the within-run and within-laboratory (total) %CV for each sample on each instrument and reagent lot combination. The estimated LoQ of the modified Access OV Monitor within-laboratory imprecision of 20% CV resulted in 0.3 U/mL. The claimed LoQ for the modified Access OV Monitor on DxI 9000 Access Immunoassay Analyzer is 2.0 U/mL.

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

CLSI guideline EP09c 3rd Edition was followed to compare the modified Access OV Monitor on DxI 9000 Access Immunoassay Analyzer to the predicate device, the Access OV Monitor on the Access 2 Immunoassay System. Patient samples falling within the analytical measuring interval of the Access OV Monitor assay were evaluated. A total of 152 serum samples were tested with three Access OV Monitor reagent lots and three calibrator lots, on three DxI 9000 Access Immunoassay Analyzers (candidate) and three Access 2 instruments (predicate). Three commercial quality controls were run in duplicate each day to verify the systems were in control. The comparison between paired measurements was analyzed using Passing-Bablok method by fitting the observed modified Access OV Monitor Assay on DxI 9000 Access Immunoassay Analyzer (dependent variable, y) into a linear regression model, with the observed values from the predicate (x, predicate). The results are summarized in the following table:

N	Range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R
152	2.4 – 5,001	0.98 (0.97; 0.99)	-0.14 (-0.38; 0.13)	1.00

2. Matrix Comparison:

Refer to K023597

C Clinical Studies:

Refer to K023597

D Clinical Cut-Off:

Refer to K023597

E Expected Values/Reference Range:

Refer to K023597

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.