510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K240403

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

Access BR Monitor

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
MOI	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 – the change of substrate and updated analytical measuring interval of the assay on the DxI 9000 Immunoassay Analyzer

B Measurand:

CA 15-3 antigen

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 BR Monitor assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of CA 15-3 antigen levels in human serum and plasma (heparin) using the Access Immunoassay Systems. This device is indicated for use in the measurement of CA 15-3 antigen to aid in the management of breast cancer patients. Serial testing for CA 15-3 antigen concentrations should be used in conjunction with other clinical methods for monitoring breast cancer.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

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

The concentration of CA 15-3 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 15-3 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 15-3 antigen values is changed, additional sequential testing should be carried out to confirm baseline values.

D Special Instrument Requirements:

DxI 9000 Access Immunoassay Analyzer (refer to K221225)

IV Device/System Characteristics:

A Device Description:

Each Access BR Monitor reagent kit contains two reagent packs (50 tests/pack). Each pack contains the following:

- Solid phase (R1a): Paramagnetic particles coated with goat anti-biotin antibodies, biotinylated anti-CA 15-3 antigen mouse monoclonal antibodies, bovine serum albumin, < 0.1% sodium azide and 0.1% ProClin 300.
- Conjugate (R1b): Mouse monoclonal anti-CA 15-3 antigen-alkaline phosphatase (bovine) conjugate, bovine serum albumin, < 0.1% sodium azide, 0.25% ProClin 300.
- Diluent (R1c): Buffered protein solution (bovine, goat, mouse), < 0.1% sodium azide, 0.1% ProClin 300.

Materials needed but not supplied with reagent kit

- Access BR Monitor Calibrators (approximately 0, 10, 50, 100, 500 and 1,000 U/mL)
- Quality Control (QC) materials: commercial control material
- Lumi-Phos PRO (substrate)
- UniCel DxI Wash Buffer II
- Access Sample Diluent A (optional)

The modification of the Access BR Monitor is:

(a) to replace substrate (Lumi-Phos 530) of the Access BR Monitor with a new substrate (Lumi-Phos PRO)
(b) to run on DxI 9000 Access Immunoassay Analyzer with an updated the analytical measuring interval of 0.8 – 1,000 U/mL.

B Principle of Operation:

The Access BR Monitor assay is a two-site immunoenzymatic "sandwich" assay. A sample is added to a reaction vessel along with mouse monoclonal anti-CA 15-3 antigen alkaline phosphatase conjugate and paramagnetic particles coated with a second mouse monoclonal anti-CA 15-3 antigen antibody. The CA 15-3 antigen in the sample binds to the immobilized monoclonal anti-CA 15-3 antigen on the solid phase, while the conjugate antibody reacts with a different antigenic site on the CA 15-3 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 BR Monitor and Access BR Monitor Calibrators on the Access Immunoassay Systems

B Predicate 510(k) Number(s):

K072612

C Comparison with Predicate(s):

Device & Predicate Device(s):	K240403	K072612 (Predicate)
Device Trade Name	Access BR Monitor	Access BR Monitor
General Device Characteristic Similarities		
Intended Use / Indications For Use	The Access BR Monitor assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of CA 15-3 antigen levels in human serum and plasma (heparin) using the Access Immunoassay Systems. This device is indicated for use in the measurement of CA 15-3 antigen to aid in the management of breast cancer patients. Serial testing for CA 15-3 antigen concentrations should be used in conjunction with other clinical methods for monitoring breast cancer.	Same
Measurand	CA 15-3	Same
Sample Type	human serum and plasma (heparin)	Same
Assay Technology	Chemiluminescent	Same
Method	Automated	Same
Measurement	Quantitative	Same
Antibody	Mouse monoclonal anti-CA 15-3	Same
Operating Principle	One-step sandwich	Same
Calibrators	Multi-point calibrators containing purified human CA-15	Same
QC Controls	Two levels	Same
Reagent Stability	Stable at 2–10°C for 56 days after initial use	Same
General Device Characteristic Differences		
Instrument	DxI 9000 Access Immunoassay Analyzer	Access 2 Immunoassay System
Substrate	Lumi-Phos PRO substrate	Access Substrate (Lumi-Phos 530)
Measuring Range	0.8 – 1,000 U/mL	0.5 – 1,000 U/mL

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-Ed2, Evaluation of the Linearity of Quantitative Measurement Procedures – Second Edition
- 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

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 within-laboratory precision was evaluated at a single site using one lot of the modified Access BR Monitor reagent on one DxI 9000 Access Immunoassay Analyzer. Seven levels of human serum samples were tested in a minimum of three replicates per run with two runs per day, over 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	Mean (U/mL)	N	Within-Run (Repeatability)		Between-Run		Between-Day		Within-Laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	4.2	126	0.1	2.0	0.1	2.8	0.00	0.0	0.1	3.4
2	19	126	0.3	1.6	0.4	2.0	0.2	1.2	0.5	2.9
3	34	120	0.8	2.2	0.6	1.7	0.6	1.6	1.1	3.2
4	79	120	1.8	2.3	1.5	2.0	0.0	0.0	2.4	3.0
5	105	120	1.9	1.8	2.4	2.3	0.0	0.0	3.1	3.0
6	425	120	9.2	2.2	9.8	2.3	0.0	0.0	13.4	3.2
7	825	120	26.3	3.2	19.9	2.4	1.8	0.2	33.0	4.0

b) Reagent Lot-to-Lot Precision:

The substrate lot-to-lot variability was assessed in K223921.

Lot-to-lot precision of the modified Access BR Monitor reagent was performed using three lots of reagents on the DxI 9000 Access Immunoassay Analyzer. Six serum samples

at different concentrations were tested in five replicates per run, one run per day over five days, resulting in N=75 data points per sample on one instrument. The same study was also performed on two additional instruments. The lot-to-lot precision on one representative instrument are summarized in the table below.

Sample	Mean (U/mL)	N	Within-Run (Repeatability)		Between-Day		Between-Reagent Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	4.3	75	0.1	2.2	0.1	2.5	0.2	3.6	0.2	4.9
2	20	75	0.3	1.7	0.4	2.2	0.8	4.0	1.0	4.9
3	30	75	0.5	1.8	0.5	1.8	1.1	3.7	1.3	4.4
4	121	75	3.0	2.5	1.2	1.0	0.0	0.0	3.2	2.7
5	229	75	4.7	2.1	4.4	1.9	0.0	0.0	6.5	2.8
6	787	75	21.7	2.8	9.9	1.3	0.1	0.0	23.9	3.0

c) *Instrument-to-Instrument Precision:*

The study was performed using three DxI 9000 Access Immunoassay Analyzers with each instrument running three lots of the modified Access BR Monitor reagent. Each study used one calibrator lot and one substrate lot. Six 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. The data of between-instrument precision using one representative lot of reagents are summarized in table below.

Sample	Mean (U/mL)	N	Within-Run (Repeatability)		Between-Day		Between-Instrument		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	4.3	75	0.1	1.9	0.1	2.4	0.3	6.6	0.3	7.3
2	20	75	0.3	1.6	0.5	2.4	1.0	4.7	1.1	5.5
3	30	75	0.6	2.1	0.5	1.8	0.8	2.7	1.2	3.9
4	123	75	2.7	2.2	1.2	1.9	1.8	1.5	3.5	2.8
5	234	75	4.6	2.0	4.3	1.8	6.1	2.6	8.8	3.8
6	795	75	19.1	2.4	14.8	1.9	14.5	1.8	28.2	3.5

2. Linearity:

Linearity of the modified Access BR Monitor on the DxI 9000 Access Immunoassay Analyzer was performed in accordance with CLSI guideline EP06, 2nd Edition. Two series of samples were prepared: one series with 10 samples for the low end of the analytical measuring interval (AMI) of the assay, the second series with nine samples for covering the entire AMI. Each dilution series were prepared by mixing one High sample with a Low sample. The Low sample was obtained from a native serum sample that was specifically depleted of CA 15-3 antigen using paramagnetic particles. The High sample used for the first series was a pool of two native serum samples with CA 15-3 at 155 U/mL and the High sample for the second series was a pool of two native serum samples with CA 15-3 at 1186 U/mL The Low sample was run in replicates of eight, and all other samples were run in replicates of four, and the mean (U/mL) of each dilution level 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. The results are summarized in table below.

Sample	Range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R^2	% Deviation* (Deviation**)
1	0.5 − 155	1.043 (1.023; 1.063)	0.016 (-0.073; 0.041)	0.998	-6% − 10% (0.01 U/mL)
2	0.4 − 1186	0.994 (0.986; 1.002)	0.003 (-0.013; 0.018)	0.999	-0.3% − 2% (0.00 U/mL)

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

** Deviation (U/mL) from Linearity for concentrations < 15 U/mL

The data support the linearity interval from 0.4 to 1186 U/mL with the deviations from linearity within ±10%. The study results support the linearity of the claimed analytical measuring interval (AMI): 0.8 – 1,000 U/mL.

3. Analytical Specificity/Interference:

   Refer to K072612

4. Assay Reportable Range:

   The reportable range is the same as the claimed measuring range: 0.8 – 1,000 U/mL.

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

   a) Traceability

   The traceability was established in K072612.

   b) Stability:

   The Access BR Monitor Reagent kit and the Lumi-Phos PRO substrate are packaged separately. The stability of the Access BR Monitor Reagent kit was established in K072612. The proposed change is to replace substrate (Lumi-Phos 530) of the Access BR 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 Limit:

   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 BR Monitor on DxI 9000 Access Immunoassay Analyzer.

   To determine LoB, the study was conducted on two DxI 9000 Immunoassay Systems with two modified Access BR Monitor reagent lots. Five analyte depleted samples (prepared from five individual native serum samples from which CA15-3 antigen was specifically depleted) were tested in five replicates per run, one run per day over three days, resulting in 75

replicates for each reagent lot and each instrument. LoB was determined as 0.1 U/mL for each of the two reagent lots based on the 95% non-parametric percentile. The claimed LoB for the modified Access BR Monitor on DxI 9000 Access Immunoassay Analyzer is 0.4 U/mL.

To determine the LoD, 10 serum samples containing low levels of CA 15-3 were run in nine replicates per run, one run per day over five days using three lots of the modified Access BR Monitor on three DxI 9000 Access Immunoassay Analyzers. LoD was calculated from LoB + "SD multiplied by the 95th percentile of the standard normal distribution" and resulted in 0.3 U/mL for each reagent lot. The claimed LoD for the modified Access BR Monitor on DxI 9000 Access Immunoassay Analyzer is 0.5 U/mL.

To determine the LoQ, 12 serum samples containing low levels of CA 15-3 were run in nine replicates per run, one run per day over five days using three lots of the modified Access BR Monitor 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 BR Monitor was set to be the CA 15-3 concentration which met the within-laboratory imprecision of 20% CV. The claimed LoQ for the modified Access BR Monitor on DxI 9000 Access Immunoassay Analyzer is 0.8 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 BR Monitor on DxI 9000 Access Immunoassay Analyzer to the predicate device, the Access BR Monitor on the Access 2 Immunoassay System. Patient samples falling within the analytical measuring interval of both Access BR Monitor assays were evaluated. A total of 163 serum samples (141 native samples from individual patients, 14 sample pools, and 8 samples spiked with antigen) were evaluated with three lots of the modified Access BR Monitor on three DxI 9000 instruments and with predicate device on three Access 2 instruments. The comparison between paired measurements was analyzed using Passing-Bablok method by fitting the observed values with the modified Access BR Monitor assay on DxI 9000 Access Immunoassay Analyzer (y, candidate) 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^2
163	0.57 − 986	0.95 (0.94; 0.96)	0.70 (0.31; 1.4)	1.00

2. Matrix Comparison:

   Refer to K072612

C Clinical Studies:

Refer to K072612

D Clinical Cut-Off:

Refer to K072612. No cutoff for Access BR Monitor monitoring has been recommended.

E Expected Values/Reference Range:

Refer to K072612

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.