510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K223921

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

Access CEA

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

B Measurand:

Carcinoembryonic antigen (CEA)

C Type of Test:

Quantitative, Chemiluminescent immunoassay

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:

The Access CEA assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of Carcinoembryonic Antigen (CEA) levels in human serum, using the Access Immunoassay Systems. CEA measured by the Access Immunoassay Systems is used as an aid in the management of cancer patients in whom changing CEA concentrations have been observed.

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 CEA in a given specimen determined with 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 CEA 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 CEA 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:

Access CEA Reagent Kit

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

- Solid phase: Paramagnetic particles coated with mouse anti-CEA MAb, suspended in TRIS buffered bovine serum albumin (BSA), with < 0.1% sodium azide and 0.1% ProClin 300
- Diluent: Phosphate buffer, protein (bovine, murine) with < 0.1% sodium azide and 0.1% ProClin 300
- Conjugate: Mouse anti-CEA MAb bound to alkaline phosphatase (bovine), diluted in phosphate buffer, protein (bovine), < 0.1% sodium azide and 0.1% ProClin 300

Materials needed but not supplied with reagent kit

- Access CEA Calibrators: at zero and approximately 1, 10, 100, 500 and 1,000 ng/mL
- Access CEA QC controls: at approximately 3 and 300 ng/mL
- Commercial control material
- Lumi-Phos PRO substrate
- UniCel DxI Wash Buffer II
- Access CEA Diluent (optional)

The modification of the Access CEA includes:

(a) to replace substrate (Lumi-Phos 530) of the Access CEA with a new substrate (Lumi-Phos PRO)
(b) to run on DxI 9000 Access Immunoassay Analyzer with the update the analytical measuring interval of 0.2 – 1,000 ng/mL

B Principle of Operation:

The Access CEA assay is a two-site immunoenzymatic "sandwich" assay using two mouse monoclonal anti-CEA antibodies (MAb) which react with different epitopes of CEA. A sample is added to a reaction vessel, along with the first anti-CEA MAb-alkaline phosphatase conjugate and the second anti-CEA MAb bound to paramagnetic particles. 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 CEA

B Predicate 510(k) Number(s):

K981985
K991707

C Comparison with Predicate(s):

Device & Predicate Device(s):	K223921 Candidate Device	K991707 Predicate	K981985 Predicate
Device Trade Name	Access CEA	Access CEA	
General Device Characteristic Similarities			
Intended Use/ Indications For Use	The Access CEA assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of Carcinoembryonic Antigen (CEA) levels in human serum, using the Access Immunoassay Systems. CEA measured by the Access Immunoassay Systems is used as an aid in the management of cancer patients in whom changing CEA concentrations have been observed.	Same	The Access CEA Immunoassay is a paramagnetic particle chemiluminescent immunoassay for the quantitative determination of carcinoembryonic antigen (CEA) in human serum using the ACCESS Immunoassay System. CEA measured by the ACCESS CEA Immunoassay, is used as an aid in the management of cancer patients.
Measurand	Carcinoembryonic antigen	Same	Same
Sample Type	Human serum	Same	Same
Assay Technology	Chemiluminescent	Same	Same
Measurement	Quantitative	Same	Same
Antibody	Monoclonal (mouse) anti-human CEA antibodies	Same	Same
Operating Principle	One-step sandwich	Same	Same
Calibrators	Multi-point calibrators containing purified human CEA	Same	Same
QC Controls	Bi-level controls containing human CEA	Same	Same
Reagent Stability	Stable at 2 to 10°C for 28 days after initial use	Same	Same
Method	Automated	Same	Same
General Device Characteristic Differences			
Instrument	DxI 9000 Access Immunoassay Analyzer	Access 2 Immunoassay System; UniCel DxI 800 Immunoassay System; UniCel DxI 600 Immunoassay System	
Substrate	Lumi-Phos PRO substrate	Access Substrate	
Measuring Range	0.2 – 1,000 ng/mL	0.1 – 1,000 ng/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 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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

All results presented below met the manufacturer's pre-determined acceptance criteria.

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 CEA reagent on one DxI 9000 Access Immunoassay Analyzer. Seven 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 (ng/mL), standard deviation (SD) (ng/mL) and percent coefficient of variation (%CV) are summarized in table below.

Sample	Mean (ng/mL)	N	Within-Run		Between-Run		Between-Day		Within-Laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.5	126	0.0	3.5	0.0	1.5	0.0	2.0	0.0	4.3
2	5.1	120	0.1	2.1	0.0	0.8	0.1	1.2	0.1	2.5
3	11.0	126	0.2	1.9	0.3	2.5	0.2	1.5	0.4	3.5
4	89.0	120	1.9	2.2	0.8	0.9	1.1	1.3	2.4	2.7
5	153	120	2.8	1.8	1.9	1.3	2.3	1.5	4.1	2.7
6	525	120	18.5	3.5	6.6	1.2	16.0	3.1	25.3	4.8
7	865	120	22.4	2.6	5.3	0.6	38.6	4.5	45.0	5.2

b) *Lot-to-Lot Precision:*

The study was performed at a single site using three modified Access CEA with three lots of Lumi-Phos PRO Substrate, three Access CEA Calibrator lots on two instruments. Six levels of human serum samples were run in five replicates per run, one run per day for two days, resulting a total of 180 datapoints for each sample. The data were analyzed for the repeatability (within-run), between-day, between-substrate lot, between-calibrator lot and total precision. The results are summarized in table below.

Sample	Mean (ng/mL)	N	Within-Run		Between-Day		Between-Substrate Lot		Between-Calibrator Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	1.0	177	0.0	0.0	0.0	3.3	0.0	2.1	0.0	0.0	0.0	4.1
2	6.0	180	0.1	1.9	0.1	1.8	0.0	0.3	0.2	2.6	0.2	3.9
3	77.0	180	1.4	1.8	1.0	1.3	1.4	1.8	1.1	1.5	2.5	3.3
4	322	180	6.1	1.9	4.8	1.5	2.3	0.7	3.7	1.1	11.0	3.4
5	609	180	12.7	2.1	13.2	2.2	11.0	1.8	4.6	0.7	22.0	3.6
6	841	180	15.6	1.9	17.7	2.1	10.5	1.2	7.0	0.8	26.7	3.2

* 3 data point were excluded due to 'instrument error'

c) *Instrument-to-Instrument Reproducibility:*

The study was performed using three DxI 9000 Access Immunoassay Analyzers with a single lot of the modified Access CEA reagent. 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. The results are summarized in table below:

Sample	Mean (ng/mL)	N	Within-Run (Repeatability)		Between-Day		Between-Instrument		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	5.4	75	0.1	1.9	0.1	1.9	0.0	0.7	0.2	2.8
2	95.0	75	1.8	1.9	0.8	0.8	1.5	1.5	2.4	2.5
3	215	75	5.9	2.7	2.5	1.1	2.9	1.3	7.0	3.3
4	475	75	10.8	2.3	6.6	1.4	5.1	1.1	13.6	2.9
5	828	75	22.3	2.7	47.4	5.7	0.0	0.0	52.4	6.3

2. Linearity:

Linearity of the modified Access CEA was performed in accordance with CLSI guideline EP06 2nd Edition. Two series of samples were prepared by mixing two High samples with Low sample span the 'analytical measuring interval' (AMI) of the modified Access CEA and to provide eight dilution levels. Low sample was obtained from a single human serum sample that was specifically stripped of CEA antigen to achieve a concentration below the low end of the AMI of the assay. Two High samples were pooled human serum with CEA concentrations of 38.63 ng/mL and 1042.74 ng/mL. 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 CEA ng/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 (ng/mL)	Slope (95% CI)	Intercept (95% CI)	R^2	% Deviation* (Deviation**)
1	0.1 − 38.6	0.952 (0.936 − 0.967)	0.003 (-0.009 − 0.015)	0.999	-7% − 5% (0.001)
2	0.1 − 1042.7	0.966 (0.950 − 0.983)	0.003 (-0.006 − 0.012)	0.999	-9% − 3% (0.00003)
Combined 1 and 2	0.1 − 1042.7	0.959 (0.949 − 0.969)	0.003 (-0.003 − 0.010)	1.000	-8% − 4% (0.000 − 0.001)

* % Deviation from Linearity for concentrations > 2.1 ng/mL
** Deviation (ng/mL) from Linearity for concentrations ≤ 2.1 ng/mL

The data support the linearity interval from 0.1 to 1042.7 ng/mL with the deviations from linearity within ±10%. The study results support the linearity of the claimed analytical measuring interval (AMI): 0.2 – 1,000 ng/mL.

3. Assay Reportable Range:

   The reportable range is the same as the claimed measuring range: 0.2 to 1,000 ng/mL.

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

   a) Traceability:

   The traceability was established in K991707.

   b) Stability:

   The Access CEA Reagent kit and the Lumi-Phos PRO substrate are packaged separately. The proposed change is to replace substrate (Lumi-Phos 530) of the Access CEA 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.

   Access CEA Reagent kit stability was established in K991707. The real-time stability study was conducted to verity the stability claims for the modified Access CEA. The results support the shelf-life of 12 months for the reagent pack stored at 2-10°C.

5. Detection Capability:

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

   LoB:
   Four blank samples (individual native serum samples from which CEA antigen was specifically depleted) were tested in five replicates per run, one run per day over three days using two modified Access CEA reagent lots (N = 60 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 0.09 ng/mL and 0.03 ng/mL. The claimed LoB for the modified Access CEA on DxI 9000 Access Immunoassay Analyzer is 0.09 ng/mL.

LoD:
Five to seven serum samples containing low levels of CEA analyte were run in nine replicates per run, one run per day over five days using three modified Access CEA reagent lots (N = minimum 225 replicates for each lot) on three 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 0.1 ng/mL for each reagent lot. The claimed LoD for the modified Access CEA on DxI 9000 Access Immunoassay Analyzer is 0.1 ng/mL.

LoQ:
Nine to eleven serum samples containing low levels of CEA analyte were run in nine replicates of per run, one run per day over five days using three modified Access CEA reagent lots (N=minimum 405 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 LoQ was set to be the CEA concentration which met the within-laboratory imprecision of 20% CV. The claimed LoQ for the modified Access CEA on DxI 9000 Access Immunoassay Analyzer is 0.2 ng/mL.

6. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

CLSI guideline EP09c 3rd Edition were followed to compare the modified Access CEA on DxI 9000 Access Immunoassay Analyzer to the predicate device, the Access CEA on the Access 2 Immunoassay System. Patient samples falling within the analytical measuring interval of the Access CEA assay were evaluated. A total of 153 deidentified serum samples were tested with three Access CEA reagent lots and three calibrator lots, using one Lumi-Phos PRO substrate lots on three DxI 9000 Access Immunoassay Analyzers (candidate) and using one Access Substrate lots on three Access 2 instruments (predicate). Two 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 CEA 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 (ng/mL)	Slope (95% CI)	Intercept (95% CI)	R
153	0.46 − 1071	0.98 (0.97 − 0.99)	0.06 (0.00 − 0.17)	1.00

2. Matrix Comparison:

Not applicable. The assay is for serum samples only.

C Clinical Studies:

Refer to K981985

D Clinical Cut-Off:

No cutoff for CEA monitoring has been recommended.

E Expected Values/Reference Range:

Refer to K981985

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.