510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K240182

B Applicant

Beckman Coulter Inc.

C Proprietary and Established Names

Access EPO

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
GGT	Class II	21 CFR 864.7250 - Erythropoietin Assay	HE - Hematology

II Submission/Device Overview:

A Purpose for Submission:

Modification of the previously cleared device

B Measurand:

Erythropoietin (EPO)

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 EPO assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of erythropoietin levels in human serum and plasma (heparin) using the Access Immunoassay Systems. This assay is intended as an aid in the diagnosis of anemias and polycythemias.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

DxI 9000 Access Immunoassay Analyzer (K221225)

IV Device/System Characteristics:

A Device Description:

The Access EPO assay consists of the reagent pack and calibrators. The reagent pack consists of three specific reagents:

- Paramagnetic particles coated with goat anti-mouse IgG: mouse anti-recombinant human EPO monoclonal antibody, bovine serum albumin (BSA), 0.1% sodium azide and 0.17% ProClin 300.
- Chicken anti-recombinant mouse EPO alkaline phosphatase (bovine) conjugate, BSA, 0.1% sodium azide and 0.17% ProClin 300.
- TRIS saline buffer containing BSA, proteins (chicken, bovine, mouse), <0.1% sodium azide and 0.17% ProClin 300.

Each Access EPO reagent kit contains two packs, 50 tests per pack, for one hundred assay determinations.

Other items needed but not supplied with reagent kit include:

Access EPO Calibrators: at zero and approximately 5, 25, 125, 375 and 750 mIU/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 EPO assay includes:

- to replace the substrate (Lumi-Phos 5530) of the Access EPO with a new substrate (Lumi-Phos PRO) and
- to run the assay on the DxI 9000 Access Immunoassay Analyzer.

B Principle of Operation:

The Access EPO assay is a two-step "sandwich" assay, where a sample is added to a reaction vessel along with the paramagnetic particles coated with mouse monoclonal anti-EPO, blocking reagent and the alkaline phosphatase conjugate. 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 reaction vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of the analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access EPO

B Predicate 510(k) Number(s):

K052223

C Comparison with Predicate(s):

Device & Predicate Device(s):	K240182	K052223
Device Trade Name	Access EPO	Access EPO
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Access EPO assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of erythropoietin levels in human serum and plasma (heparin) using the Access Immunoassay Systems. This assay is intended as an aid in the diagnosis of anemias and polycythemias.	The Access EPO assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of erythropoietin levels in human serum and plasma (heparin) using the Access Immunoassay Systems. This assay is intended as an aid in the diagnosis of anemias and polycythemias. With the

		advent of the administration of recombinant erythropoietin as a biologic therapy to increase red blood cell mass, an erythropoietin assay may be used also to aid in the prediction and monitoring of response to recombinant erythropoietin treatment in persons with anemias. The Access EPO calibrators are intended to calibrate the Access EPO assay for the quantitative determination of EPO levels in human serum and plasma (heparin) using the Access Immunoassay Systems.
Assay technology	Two-step chemiluminescent immunoenzymatic sandwich	same
Calibrators	Access EPO calibrators, 0, 5, 25, 125, 375, 750 mIU/mL	same
Measuring interval	0.6–750 mIU/mL	same
Quality Control (QC)	Commercial control material	same
Storage conditions	Reagent stored at 2–10ºC	
Expected range	2.59–18.50 mIU/mL	same
Traceability	WHO Second IRP (67/343)	same
Calibration frequency	28 days	same
Sample type	Serum and plasma (heparin)	same
General Device Characteristic Differences		
Substrate	Lumi-Phos pro substrate	Access substrate
Instrument	DxI 9000 Access Immunoassay Analyzer	Access Immunoassay system ((Access, Access 2, Synchron LXi 725,

		UniCel DxI 800, UniCel DxC 600i)

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Third Edition

CLSI EP06-2nd Edition-: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

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

CLSI EP09c 3rd Edition: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Third 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:

a. Within-Laboratory Precision

Precision studies were performed at a single site on three DxI 9000 Immunoassay analyzers using three reagent lots and three calibrator lots based on CLSI EP 05-A3. Five samples were run in duplicate, two runs per day over 20 or more days. The five samples tested were one sample pool of native and stripped serum sample, two samples were a pool of native serum samples, and two samples were a pool of serum spiked with purified EPO antigen. Repeatability (within-run), between-run, between-day, between-lot/instrument and within-laboratory were evaluated. The mean (mIU/mL), standard deviation (SD) and percent coefficient of variation (%CV) are summarized below.

Sample	N	Mean (mIU/mL)	Within-Run		Between-Run		Between-Day		Between-Lot /Instrument		Within-Lab	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	240	1.8	0.04	2.1	0.02	0.8	0.04	2.0	0.06	3.5	0.08	4.6
2	240	18	0.3	1.5	0.2	0.9	0.3	1.8	1.2	6.8	1.3	7.2
3	240	79	1.4	1.8	0.2	0.3	1.5	1.9	4.2	5.3	4.7	6.0
4	240	231	5.4	2.3	1.2	0.5	4.2	1.8	11.3	4.9	13.2	5.7
5	240	582	12.8	2.2	0	0.0	14.4	2.5	34.5	5.9	39.5	6.8

Precision was repeated with additional native samples at additional concentrations spanning the assay analytical measuring range. A panel of three individual native serum samples, a native serum pool of individual samples of similar concentrations (sample 4) and a native serum pool supplemented with EPO antigen (sample 5) were tested. The

study was run on one analyzer using one reagent lot and one calibrator lot. Samples were tested in duplicate with two runs per day over 20 days.

Sample	N	Mean (mIU/mL)	Within-Run		Between-Run		Between-Day		Within Laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	80	267	4.9	1.8	1.2	0.4	3.8	1.4	6.3	2.4
2	80	2.0	0.05	2.3	0.02	1.0	0.06	2.8	0.07	3.8
3	80	105	2.2	2.2	1.0	1.0	1.4	1.4	2.8	2.7
4	80	18	0.2	1.2	0.1	0.5	0.5	2.7	0.5	3.0
5	80	548	9.3	1.7	0.0	0.003	18.1	3.3	20.4	3.7

b. *Instrument-to-Instrument Reproducibility*

Reproducibility was performed based on CLSI EP05-A3. Five samples at different concentrations were run on three analyzers across three reagent lots and one calibrator lot on each instrument with five replicates per run and one run per day over five days. The five samples were prepared as follows: Sample 1 is a pool of two individual native serum samples and one ultrafiltered sample, Sample 2 is a pool of two individual native serum samples of similar concentration, Sample 3 is a pool of individual native serum samples, Sample 4 and Sample 5 are both a pool of two individual native serum samples supplemented with purified recombinant human EPO antigen. The data was used to calculate between-run, between-day, between-lot, between-instrument, and reproducibility (total precision). The mean (mIU/mL), standard deviation (SD) and percent coefficient of variation (%CV) are summarized below.

Sample	N	Mean mIU/mL	Within-Run		Between-Day		Between-Lot		Between-Instrument		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	225	1.9	0.03	1.7	0.02	1.2	0.03	1.5	0.02	1.1	0.05	2.8
2	225	19	0.3	1.8	0.2	1.0	1.3	6.7	0.4	2.2	1.4	7.4
3	225	80	1.5	1.9	0.9	1.1	4.1	5.2	1.8	2.3	4.8	6.1
4	225	236	4.8	2.0	4.1	1.7	6.7	2.8	5.7	2.4	10.8	4.6
5	225	594	13.8	2.3	12.3	2.1	21.3	3.6	15.5	2.6	32.2	5.4

An additional instrument-to-instrument reproducibility was repeated with additional native samples at additional concentrations spanning the assay analytical measuring range. A panel of three individual native serum samples, a native serum pool of individual samples of similar concentrations (sample 4) and a native serum pool supplemented with EPO antigen (sample 5) were tested. The study was run on three analyzers using one reagent lot and one calibrator lot. Samples were tested in replicates of five per run, with one run per day over five days on each instrument.

Sample	N	Mean mIU/mL	Within-Run		Between-Day		Between-Instrument		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	75	265	5.5	2.1	2.3	0.9	3.3	1.3	6.8	2.6
2	75	2.1	0.04	1.9	0.16	8.0	0.02	1.0	0.17	8.3
3	75	102	2.0	2.0	0.9	0.9	1.7	1.7	2.8	2.7
4	75	17	0.3	1.7	0.2	1.4	0.4	2.3	0.6	3.2
5	75	569	16.7	2.9	16.2	2.8	15.3	2.7	27.9	4.9

c. Lot-to-lot Calibrator Precision

The study was performed with a panel of three native serum samples at concentrations spanning the Access EPO analytical measuring range. All samples were tested on one DxI 9000 instrument, across three Access EPO calibrator lots, and one Access EPO reagent lot. Three calibrations were performed on each calibrator lot. Each sample was tested in replicates of two per run with two runs per day over 15 days. Three quality controls were run in duplicate on each day to ensure systems were in control.

Sample	N	Mean mIU/mL	Within-Run		Between-Day		Between-Run		Between-Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	540	2.0	0.04	2.2	0.05	2.4	0.04	1.8	0.04	2.0	0.085	4.2
2	540	108	2.16	2.0	1.12	1.0	1.83	1.7	2.39	2.2	3.87	3.6
3	540	277	5.36	1.9	3.44	1.2	3.70	1.3	7.58	2.7	10.57	3.8

2. Linearity:

A linearity study was performed based on CLSI EP06, 2nd Edition. A low sample was obtained from a single native sample that was specifically depleted of EPO antigen using paramagnetic particles. A high sample consisting of a pool of seven native serum samples with similar concentration was prepared to represent the upper end of the measuring interval. A panel of seven samples were prepared using the high and low samples. The low sample was run in replicates of eight, all other samples were run in replicates of four. The study was run on one analyzer using one reagent lot and one calibrator lot. Three quality controls were run in replicates of two.

An additional verification study was performed to evaluate linearity of the low end of the measuring range. A low sample was obtained from a single native sample that was specifically depleted of EPO antigen using paramagnetic particles. A high individual native sample at a concentration of approximately 100 mIU/mL was also acquired. Eight samples were prepared for testing. The low sample was run in replicates of eight, all other samples were run in replicated of four.

Linearity was established for the analytical measuring interval of 0.6–750 mIU/mL.

3. Analytical Specificity/Interference:

Refer to K052223.

4. Assay Reportable Range:

0.6–750 mIU/mL

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

Traceability and stability of Access EPO were established in K052223.

The shelf-life claims and on-board (DxI 9000 Access Immunoassay analyzer) 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 Access EPO.

LoB: Samples were run on two analyzers with two reagent lots and one calibrator lot. Five unique individual native serum samples from which EPO antigen was depleted using paramagnetic particles were tested over three days, one run per day, five replicates per run, for each pack lot. Three QC samples in replicates of two were run each day. The LoB was calculated for each reagent lot based on a non-parametric approach. The claimed LoB for the Access EPO assay on the DxI 9000 Access Immunoassay analyzer is 0.6 mIU/mL.

LoD: Samples were run on three analyzers with three reagent lots and one calibrator lot. Six serum samples containing low levels of EPO analyte were tested over five days with one run per day and nine replicates per run for each pack lot. The claimed LoD for the Access EPO assay on DxI 9000 Access Immunoassay Analyzer in 0.6 mIU/mL.

LoQ: Samples were run on three analyzers with three reagent lots and one calibrator lot. Thirteen serum samples containing low levels of EPO analyte were measured. Samples were testing in replicates of nine per run with one run per day and five total days on each pack lot and instrument. The claimed LoQ for the Access EPO assay on DxI 9000 Access Immunoassay Analyzer is 0.6 mIU/mL.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The method comparison study was performed to compare the Access EPO assay on the DxI 9000 Immunoassay analyzer to the predicate device, the Access EPO assay on the Access 2 Immunoassay System. A total of 152 samples were evaluated, of which 133 were native serum samples, 8 were pools of native serum samples, and 11 were native serum samples supplemented with EPO antigen. The study was run on three DxI 9000 Access Immunoassay analyzers and three Access 2 analyzers with three reagent pack lots and three calibrator lots. Two commercial quality controls were run in duplicate each day. The comparison between paired measurements was analyzed using Passing-Bablok method. The study met pre-defined acceptance criteria.

N	Range (mIU/mL)	Slope (95% CI)	Intercept (95% CI)	R
152	0.73–680	0.99 (0.97, 1.00)	-0.040 (-0.19, 0.22)	1.00

2. Matrix Comparison:

Refer to K052223

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable

2. Clinical Specificity:

Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Refer to K052223

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.