510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K162208

B. Purpose for Submission:

The sponsor selected a representative analyte assay (IgG Reagent) to demonstrate that these previously cleared reagents have the same performance characteristics on the new DxC 700 AU analyzer as compared to the previously marketed AU series of chemistry analyzers. There are no changes to the formulation or performance characteristics of the IgG reagent.

C. Measurand:

Immunoglobulin G (IgG)

D. Type of Test:

Quantitative immunoturbimetric assay

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

IgG

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.5510 Immunoglobulins A, G, M, D, E Immunological Test System

2. Classification:

   Class II

3. Product code:

   CFN: Method, Nephelometric, Immunoglobulins (G, A, M)

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

   Same as indications for use below.

2. Indication(s) for use:

   System reagent for the quantitative determination of IgG immunoglobulins in human serum, plasma and cerebrospinal fluid on Beckman Coulter AU analyzers. The measurement of IgG aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   DxC 700 AU Clinical Chemistry Analyzer

   The DxC 700 AU Clinical Chemistry Analyzer is a family member of the AU series of analyzers, including the AU5800 (K112412). The devices have same/similar design and modes of operation. The instrument was reviewed and cleared in K161837.

   Hardware, Software and System feature comparisons for the Beckman Coulter DxC 700 AU Clinical Chemistry Analyzer with the AU5800 analyzer is included in K161837. This is a fully automated, random access chemistry analyzer used for analysis of serum, plasma, urine, CSF, and other body fluids. The DxC 700 AU clinical chemistry analyzer measures analytes in samples using the same reagents, calibrators, quality control materials and other consumables used within the AU series of instruments.

I. Device Description:

The device consists of two reagents: R1 buffer (Tris buffer pH 7.2, polyethylene glycol 6000) and R2 (goat anti-IgG antiserum). The reagents contain sodium azide as preservative.

Reagent (for Serum/Plasma Application)

- Tris buffer pH 7.2 48 mmol/L
- Polyethylene glycol 6000 3.1%
- Goat anti-IgG antiserum Dependent on titre

Reagent (for CSF Application)

- Tris buffer pH 7.2 mmol/L
- Polyethylene glycol 6000 4.9%

- Goat anti-IgG antiserum Dependent on titre

J. Substantial Equivalence Information:

1. Predicate device name:

   Olympus IgG reagent on the AU5800 Clinical Chemistry Analyzer

2. Predicate 510(k) number:

   K073490

3. Comparison with predicate:

   There are no differences in the formulation or performance characteristics between the candidate IgG reagent and the predicate IgG reagent.

Similarities		
Item	Predicate Device Olympus IgG Reagent on AU5800 Clinical Chemistry Analyzer (K073490)	Candidate Predicate IgG Reagent on DxC 700 AU Clinical Chemistry Analyzer
Intended Use	System reagent for the quantitative determination of IgG immunoglobulins in human serum, plasma and cerebrospinal fluid on Beckman Coulter AU analyzers. The measurement of IgG aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.	Same
Measurment	Quantitative	Same
Methodology	Immunoturbidimetric	Same
Antibody	Goat anti-IgG	Same
Reagent form and storage	Liquid, on-board storage	Same
Specimen Type	Serum, EDTA or Lithium heparin plasma, and cerebrospinal fluid	Same
Calibrator	Serum Protein Multi-Point Calibrator (Cat # ODR3021)	Same
On-board reagent stability	90 days	Same
Calibration stability	Serum, plasma 90 days CSF, two days	Same
Analytic Range	Serum/plasma:	Same

Similarities		
Item	Predicate Device Olympus IgG Reagent on AU5800 Clinical Chemistry Analyzer (K073490)	Candidate Predicate IgG Reagent on DxC 700 AU Clinical Chemistry Analyzer
	75–3000 mg/dL CSF: 2–50 mg/dL	Same
LoQ	Serum/ plasma: 75mg/dL CSF: 2 mg/dL	Same Same
Traceability	Preparation CRM 470	Same

Differences		
Item	Predicate Device Olympus IgG Reagent on AU5800 Clinical Chemistry Analyzer (K073490)	Candidate IgG Reagent on DxC 700 AU Clinical Chemistry Analyzer
Instrument Required	AU400/400e/480, AU600/640/640e/680 and AU2700/5400/AU5800 Beckman Coulter Analyzers	AU400/400e/480, AU600/640/640e/680, AU2700/5400/AU5800 and **DxC 700 AU Beckman Coulter Analyzers**

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A3 "Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition"

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

CLSI EP07-A2: "Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition"

CLSI EP09-A3: "Measurment Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline Third Edition"

CLSI guideline EP17-A2 "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures Approved Guideline - Second Edition"

CLSI guideline EP28-A3c "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition"

CLSI EP25-A "Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline"

L. Test Principle:

The AU IgG assay is a reagent for the quantitative determination of IgG immunoglobulins in human serum, plasma and cerebrospinal fluid on Beckman Coulter AU analyzers.

When a sample is mixed with R1 buffer and R2 antiserum solution, human IgG reacts specifically with anti-human IgG antibodies to yield insoluble aggregates. Immune complexes formed in solution scatter light in proportion to their size, shape and concentration. Turbidimeters measure the reduction of incident light due to reflection, absorption or scatter. The decrease in intensity of light transmitted (increase in absorbance) through particles suspended in solution is as a result of complexes formed during the antigen-antibody reaction.

M. Performance Characteristics:

1. Analytical performance:

IgG assay was selected to provide a representative immunoturbidimetry assay on the DxC 700 AU Clinical Chemistry Analyzer. In order to demonstrate the comparability between the predicate device, the IgG assay used on the AU5800 instrument, and the candidate device, the IgG assay used on the DxC 700 AU instrument, the following performance testing was conducted:

- Precision
- Auto-dilution
- Linearity
- Prozone (hook effect)
- In use (On board) Stability and Calibrator Stability
- Sensitivity
- Reference Interval
- Interference
- Method Comparison

a. Precision/Reproducibility:

Repeatability:

Repeatability (within-run) and within-laboratory (total) precision studies were performed using pooled samples and passed the companies pre-defined acceptance criteria.

Serum precision was performed by testing six serum and three CSF samples across the assay range, two runs per day in duplicate for 20 days (n=80). The results are summarized in the tables below:

Precision in serum samples:

Concentration	Repeatability (Within-Run)		Within-laboratory (Total)	
mg/mL	SD	%CV	SD	%CV
149.6	1.6	1.1	4.2	2.8
486.0	3.5	0.7	6.6	1.4
875.9	8.5	0.9	10.7	1.2
1830.9	28.1	1.5	29.1	1.6
2163.2	41.4	1.9	41.1	1.9
2763.1	73.3	2.7	73.3	2.7

Precision in CSF samples:

Concentration	Repeatability Within Run		Within Laboratory (Total)	
Mg/mL	SD	%CV	SD	%CV
4.4	0.1	2.8	0.2	4.2
9.8	0.1	1.2	0.2	1.9
34.8	0.3	0.9	0.6	1.9

Automatic Dilution:

A study was performed to verify the automatic dilution settings on the DxC 700 AU Clinical Chemistry Analyzer. The accuracy of automatic sample pre-dilution was tested by comparing manual dilution with the instrument's 1:10 auto dilution function. Samples were tested using one lot of serum IgG reagent and one lot of calibrators. Serum pools with concentration of approximately 4000mg/dL, 5000mg/dL and 6000 mg/dL pools were diluted 1:10 with 0.9% saline manually or by the instrument, and the diluted pools were run in 20 replicates (n=20). The results passed the companies pre-defined acceptance criteria. The results are summarized below:

	Manual Dilution		Auto-Dilution		Bias Manual vs Auto Dilution
Serum Concentration	SD mg/dL	%CV	SD mg/dL	%CV	
4000 mg/dL	3.1	0.8	4.8	1.2	-3%
5000 mg/dL	2.9	0.6	3.4	0.7	-5%
6000 mg/dL	3.2	0.6	4.9	0.9	-8%

Autodilution is not recommended for CSF samples.

Instrument precision:

Precision studies were carried out on three DxC 700 AU analyzers
using one lot of reagent and one lot of calibrator for IgG with six pooled serum and three pooled CSF samples. The experimental design utilized 5 replicates, once a day,

over five days (n=25) for each sample. The same samples were run on all three analyzers.

Instrument to instrument IgG Serum:

	Pool 1 mg/dL	Pool 2 mg/dL	Pool 3 mg/dL	Pool 4 mg/dL	Pool 5 mg/dL	Pool 6 mg/dL
Instr 1 (Mean)	150.4	530.4	972.2	1866.4	2246.9	2656.3
Instr 2 (Mean)	150.9	535.8	980.6	1880.1	2267.5	2709.7
Instr 3 (Mean)	151.2	528.9	956.3	1830.4	2196.5	2611.8
Total Mean	150.8	531.7	969.7	1858.9	2237.0	2659.2
SD	0.4	3.7	12.3	25.7	36.5	49.0
CV%	0.3	0.7	1.3	1.4	1.6	1.8

Instrument to instrument IgG CSF:

	Pool 1 mg/dL	Pool 2 mg/dL	Pool 3 mg/dL
Instr 1 (Mean)	4.6	10.4	32.9
Instr 2 (Mean)	4.6	10.4	32.8
Instr 3 (Mean)	4.6	10.3	33.0
Total (Mean)	4.6	10.4	32.9
SD	0.0	0.1	0.1
CV%	0.8	0.5	0.2

b. Linearity/assay reportable range:

Linearity:

Serum and CSF samples spiked with human gamma globulin were used to evaluate linearity. High concentration and low concentration pools were combined to created dilutions across the analytical measuring range. Dilutions were assayed in quadruplicate.

Linearity studies met the companies predefined acceptance criteria. The results are summarized in the table below:

	Samples mg/dL	Linear range mg/dL	Results	% Recovery
Serum	48.36 to 3221.71	75–3000 mg/dL	Slope: 1.000 Intercept: 5.802 R: 0.9996	97.7%–103.4%
CSF	0.43 to 61.18	2–50 mg/dL	Slope: 0.9951 Intercept: 0.2021 R: 0.9990	93.2%–113.4

The measuring range for the serum IgG assay is 75–3000 mg/dL.
The measuring range for the CSF IgG assay is 2-50 mg/dL.

Prozone/Hook Effect:

A study was done to verify the prozone performance on the DxC 700 AU and to confirm that the data applicable to the predicate device (AU5800) also applies to the DxC 700 AU. Three samples with a high concentration of analyte were diluted to get concentrations from the claimed prozone to within the measuring range. No hook effect was seen at the following concentrations:

Matrix	Prozone
Serum	>30,000 mg/dL
CSF	>6000 mg/dL

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:

Traceability was not provided. The calibrator is the same as in the predicate and is traceable to the International Reference Preparation CRM470 (US designation RPPHS lot 91/0619).

Stability:

In-Use Reagent and Calibration Stability Verification study was performed. The objective of the study was to verify the on-board claim for the IgG reagents on the DxC 700 AU analyzer. The stability of the reagents is the same as in the predicate device (K073490). The results of the Reagent In-Use and Calibration Stability studies are presented in the table below:

	Stability Claim (Days)	
Sample type	Onboard Stability	Calibration Stability
Serum/Plasma	90	90
CSF	90	2

d. *Detection limit:*

LoB, LoD and LoQ studies were carried out on the DxC 700 AU using two lots of reagent and one lot of calibrator across multiple days. Four blank samples run in five replicates for three days and seven low level samples run in five replicates for eight days were tested for a total of 60 blank replicates and 280 low-level sample replicates per reagent lot. This was done for the both serum and CSF samples. The results are summarized below:

Sample	Measuring Range (mg/dL)	LoB (mg/dL)	LoD (mg/dL)	LoQ (mg/dL)
Serum	75–3000	20.26	23.36	29.47
CSF	2–50	0.83	1.18	1.28

e. Analytical specificity:

Analytical specificity was tested by adding potential interfering substances to patient samples or pools to determine the magnitude of the effect. Different concentrations of interferents were tested in quadruplicate at two concentrations of the analyte on the Beckman Coulter DxC700 AU Clinical Chemistry Analyser using one lot of reagent and one lot of calibrator. The difference in recovery of the samples with and without the potential interfering substances was calculated. Similar to the predicate device, there is no interference up to the concentration levels indicated in the table below:

Substance	Serum	CSF
Bilirubin	40 mg/dL	36 mg/dL
Lipids	1000 mg/dL	Not tested
Hemoglobin	500 mg/dL	500 mg/dL
RF	1200 IU/mL	Not tested

f. Assay cut-off:
See reference range

2. Comparison studies:

a. Method comparison with predicate device:

The study included 128 serum and 108 CSF samples that were within the assay's measuring range. Samples were tested on on a DxC 700 AU instrument and compared to the predicate instrument, AU5800. The study was done in duplicates and regression analysis was performed using only the first replicate result. The results were summarized in the table below:

	IgG (Serum)	IgG (CSF) (95%CI)
AMR	75–3000 mg/dL	2–50 mg/dL
Slope	0.986 (95%CI 0.974–0.997)	1.002 (95%CI 0.996–1.008)
Interrcept	21.348 (95%CI 7.253–35.443)	-0.055 (95%CI (−0.160)–0.050)
R	0.998	0.999
N	129	107
AU5800 Sample Range(Method X)	85.61- 2945.65 mg/dL	2.29- 48.03 mg/dL
DxC 700 AU Sample Range (Method Y)	75.50-2936.27 mg/dL	2.21- 47.88 mg/dL

b. Matrix comparison:

A study was done to demonstrate comparable performance between serum and plasma samples (EDTA and Lithium-Heparin). 55 sets of matched samples were included in the analysis, using one lot of IgG reagent and one lot of calibrator. The serum results from the IgG test was compared to the corresponding EDTA and Lithium-Heparin plasma results from the same donor. Samples were run in duplicates and analyzed using only the first replicate result. Data was analysed using Weighted Deming regression. The results passed the company's pre-defined acceptance criteria and are summarized in the table below:
Serum vs plasma matrix comparison:

Anticoagulant	# of Samples	Sample Range (mg/dL)	Regression analysis
EDTA	55	88.49 – 2992.39	Slope:0.985 (95%CI 0.974-0.995) Intercept: -7.521 (95%CI (-16.372)-1.258) R: 0.999
Lithium Heparin	55	88.49 – 2992.39	Slope: 0.997 (95%CI 0.986-1.009 Intercept: -8.752 (95%CI (-18.425)-0.834 R: 0.999

3. Clinical studies:

a. Clinical Sensitivity:
Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data:
Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

A reference range verification study was performed using fresh serum from 25 healthy volunteers. Samples were run in duplicate on the DxC 700 AU system using two lots of IgG reagent. The serum reference range is verified as the same as in the predicate device and are summarized below:

Sample Type	Reference Range	Age
Serum	635-1741mg/dL	N/A
*CSF	3.5 mg/dL ± 2.0 mg/dL	15 – 20 y
	4.2 mg/dL ± 1.4 mg/dL	21 – 40 y
	4.7 mg/dL ± 1.0 mg/dL	41 – 60 y

*The CSF reference range is based on literature: Painter PC, Cope JY, Smith JL Reference information for the clinical laboratory. In: Burtis CA, Ashwood ER, eds.Tietz textbook of clinical chemistry,Philadelphia: WB Saunders Company,1999; 1820pp

The device labeling includes a recommendation that each laboratory should determine its own expected values as directed by good laboratory practice.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.