510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k130122

B. Purpose for Submission:

Modification to cleared device (k993547)

C. Measurand:

Immunoglobulin M

D. Type of Test:

Quantitative, Nephelometric

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

IMMAGE® Immunochemistry System Low Concentration Immunoglobulin M (IGMLC) Reagent
IMMAGE® Immunochemistry Systems CSF-CAL Cerebrospinal Fluid Protein Calibrator

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.5510, Immunoglobulins A, G, M, D, and E immunological test system
   21 CFR §862.1150, Calibrator

2. Classification:

   Class 2

3. Product code:

   CFN – Method, Nephelometric, Immunoglobulins (G, A, M)
   JIX – Calibrator, Multi-Analyte Mixture

4. Panel:

   Immunology (82)
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   IMMAGE® Immunochemistry System Low Concentration Immunoglobulin M (IGMLC) Reagent:

   IMMAGE® Immunochemistry Systems IGMLC Reagent, when used in conjunction with IMMAGE® Immunochemistry Systems and Cerebrospinal Fluid Protein Calibrator, is intended for quantitative determination of Immunoglobulin M (IGMLC) in human serum or cerebrospinal fluid (CSF) by rate nephelometry.

   IMMAGE® Immunochemistry Systems CSF-CAL Cerebrospinal Fluid Protein Calibrator:

   CSF CAL (Cerebrospinal Fluid Protein Calibrator), when used in conjunction with Beckman Coulter Low Concentration Immunoglobulin A (IGALC) and Low Concentration Immunoglobulin M (IGMLC) reagents is intended for use on IMMAGE for the calibration of these reagents.

2. Indication(s) for use:

   Same as above

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   IMMAGE Immunochemistry Systems

I. Device Description:

The IMMAGE® Immunochemistry System Low Concentration Immunoglobulin M (IGMLC) Reagent kit includes (a) one IGMLC Cartridge containing IGMLC Particle Reagent (particle bound anti-IgM), Antigen Excess Solution (processed diluted human serum), sodium azide (used as a preservative) and bovine serum albumin and non-reactive chemicals, (b) two Evaporation Caps, and (c) one IGMLC Reagent Bar Code Card.

The Beckman Coulter Cerebrospinal Fluid Protein Calibrator (CSF CAL) components include (a) Cerebrospinal Fluid Protein Calibrator, (b) Cerebrospinal Fluid Protein Calibrator Bar Code Card, (c) Cerebrospinal Fluid Protein Calibrator Bar Code Strips, and (d) Value Assignment Sheet.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s):
   Beckman Coulter IMMAGE Immunochemistry System Low Concentration Immunoglobulin M (IGMLC) Reagent and Beckman Coulter Cerebrospinal Fluid Protein Calibrator (CSF CAL); (k993547)

2. Comparison with predicate:

Similarities		
Item	Device IGMLC Reagent and Calibrator (k130122)	Predicate IGMLC Reagent and Calibrator (k993547)
Intended Use:	IGMLC reagent is intended for the quantitative determination of immunoglobulin M (IGMLC) in human serum or cerebrospinal fluid (CSF) by rate nephelometry. CSF CAL is intended for use on IMMAGE for the calibration of these reagents.	Same
Instrument	IMMAGE Immunochemistry Systems	Same
Technology	Rate nephelometric method	Same
Result Output	Quantitative result based on calibration curve	Same
Calibrator Formulation	Prepared from human urine to which immunoglobulin A and immunoglobulin M have been added	Same
Specimen types	Serum, CSF	Same

Differences		
Item	Device IGMLC Reagent and Calibrator (k130122)	Predicate IGMLC Reagent and Calibrator (k993547)
Analytical Sensitivity	CSF: 0.15 mg/L Serum: 32.4 mg/L	CSF: 0.3 mg/L Serum: 64.8 mg/L
Calibrator traceability	IFCC Reference preparation ERM-DA470(k)/IFCC	IFCC Reference preparation CRM 470
Analytical Range	CSF 0.15 - 10 mg/L Serum 32.4 - 2160 mg/L	CSF 0.3 - 10 mg/L Serum 64.8 - 2160 mg/L
Equivalency	Comparison to the Predicate assay	Concordance to IFE method
Internal Standards	Two additional internal standard levels were added to the internal standard curve at the low end	

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

EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline, Second Edition

EP06-A, Evaluation of Linearity of Quantitative Measurement, Approved Guideline, Second Edition

EP09-A2, Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition

EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantification, Approved Guideline

EN ISO 17511: In vitro diagnostic medical devices. Measurement of quantities in biological samples. Metrological traceability of values assigned to calibrators and control materials

L. Test Principle:

The IGMLC test measures the rate of increase in light scattered from particles suspended in solution as a result of complexes formed during an antigen-antibody reaction. A beam of light is passed through the cuvette and, as the antigen-antibody reaction proceeds, the light passing through the cuvette is scattered increasingly as insoluble immune complexes are formed. The light scatter is monitored by measuring the light intensity at an angle away from incident light. The IGMLC Reagent and CSF Calibrator are designed for optimal performance on the IMMAGE Immunochemistry Systems. A curve fit model is applied to the assay result to create parameters that allow each reagent lot to have its own unique stored curve. For a CSF sample, the instrument will use a 50 µL sample size and concentration will

read directly from the stored curve. For a serum sample, the instrument will make 1:39 dilution and pick up 8 µL of sample and then multiply result by 216.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision testing was performed in accordance with CLSI EP5-A2. Three separate serum sample pools representing low (32.4 – 43.4 mg/L; Serum-1), mid (432 – 1296 mg/L; Serum-2) and high (1728 – 2160 mg/L; Serum-3) range, and CSF samples pools representing low (0.15 – 0.20 mg/L; CSF-1), mid (2 – 6 mg/L; CSF-2) and high (8 – 10 mg/L; CSF-3) range were included in the study. The experimental design utilized duplicate sample analysis, twice daily, over the course of twenty working days (n=80). The data were analyzed for within-run, between-run, between-day, and total precision and the mean U/mL and percent coefficient of variation (%CV) are summarized below.

Sample	N	Mean) (mg/L)	Within-Run		Between Run		Between Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
CSF-1	80	0.196	0.03	16.55%	0	0%	0.01	4.57%	0.03	15.64%
CSF-2	80	2.49	0.05	2.07%	0.06	2.22%	0	0%	0.07	2.85%
CSF-3	80	8.81	0.29	3.25%	0.29	3.32%	0	0%	0.38	4.30%
Serum-1	80	38.5	3.84	9.99%	0.69	1.80%	1.46	3.81%	4.17	10.84%
Serum-2	80	1250.1	28.87	2.31%	21.33	1.71%	0	0%	35.59	2.85%
Serum-3	80	1935.8	55.23	2.85%	29.58	1.53%	10.23	0.53%	63.48	3.28%

b. Linearity/assay reportable range:

Linearity studies were conducted in accordance with CLSI Guideline EP06-A, Evaluation of Linearity of Quantitative Measurement, Approved Guideline, Second Edition. Two sample sources, including internal standards traceable to ERM-DA470k/IFCC and patient sample pools, were used to demonstrate linearity. Each sample and dilution was evaluated in replicates of five.

The linear regression parameters (slope, intercept and r^2) of the observed values vs. predicted values are shown below.

Sample type	Sample	Dilution range (mg/L)	Slope	Intercept	r^2
Serum	Low-1	29.70 – 297.01	0.977	6.918	0.999
	Low-2	29.72 – 297.20	0.999	2.340	0.997
	Low-3	30.51 – 305.12	0.970	5.538	0.999
	High-1	341.40 – 1707.02	1.033	34.837	0.998

Sample type	Sample	Dilution range (mg/L)	Slope	Intercept	r^2
	High-2	354.68 – 1773.39	1.019	22.365	0.999
	High-3	386.35 – 1931.75	1.034	58.827	0.999
CSF	Low-1	0.13 – 1.33	1.073	-0.110	0.997
	Low-2	0.15 – 1.52	1.012	-0.030	0.999
	Low-3	0.15 – 1.50	1.006	-0.011	0.999
	High-1	1.74 – 8.70	0.986	-0.002	0.998
	High-2	1.73 – 8.63	0.985	0.088	0.999
	High-3	1.74 – 8.72	0.992	0.033	0.999

The claimed reportable Analytical Measuring range is shown in the table below:

IgM Assay	Assay reportable range
Serum	32.4 – 2160 mg/L
CSF	0.15 – 10 mg/L

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

Traceability: The IMMAGE system uses a stored response curve that is created during manufacture by diluting single-level internal standard which is traceable to the IFCC reference preparation to plasma protein, material ERM-DA470k/IFCC. The traceability process is based on EN ISO 17511. The curve is established using multiple instruments. A curve fit model is applied to the assay result to create parameters that allow each reagent lot to have its own unique stored curve. The single point calibrator is also value assigned using the same internal standard that is used for the stored curve.

Reagent Stability: No change (referred to k993547).

d. Detection limit:

Limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined in accordance with CLSI EP17-A.

LoB: For serum, four patient sample pools created from IgM negative sera were assayed daily in replicates of 5 for a period of three days (total 60 data points) on two instruments. For CSF, CSF diluent was assayed daily in replicates of 5 for a period of three days (total 15 data points) on two instruments. Datasets were ranked from lowest to highest for these blank readings and the 95th percentile reading was determined from this ranking.

LoD: For serum, four pools created from a serum patient sample and IgM depleted human serum at a mean value ≤ 32.4 mg/L and assayed daily in replicates of 5 for a

period of three days (total 60 data points) on two instruments. For CSF, four pools patient sample pools at a mean value ≤ 0.15 mg/L created from a CSF patient sample pool and CSF diluent were assayed daily in replicates of 5 for a period of three days (total 60 data points) on two instruments.

LoQ: In order to establish LoQ for serum and CSF, three low-concentration IgM pools were run over 2 reagents lots and 2 instruments. For serum, there were a total of 45 replicates, 3 reps per pool, 3 pools, and 5 runs. For CSF, there were a total of 40 replicates from 3 pools: 3 reps for two of the pools and 2 reps for the third pool, and 5 total runs. The LoQ samples were created from an internal standard with a known value.

IgM assay	LoB (mg/L)	LoD (mg/L)	LoQ (mg/L)
Serum	7.46	18.05	32.4
CSF	0	0.0586	0.13

e. Analytical specificity:

Established in k993547.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison and bias estimation experiments were designed using CLSI guideline EP09-A2. The testing compared IGMLC pre-design change lots and IGMLC design changed lots. Eighty (80) CSF and serum specimens with IgM concentrations spanning the analytical ranges of the two sample types were obtained from commercial sources, including paired CSF and serum patient samples from clinical laboratories and commercial sources. About 5% CSF samples (4 of 80 samples) and 12.5% of the serum samples (10 of 80 samples) were contrived. The method comparison samples were tested internally over multiple days; one run per day with eight of each of the sample types (CSF and Serum) per day, over a period of 10 days. The IgM values in CSF samples ranged from 0.150 to 8.982 mg/mL while IgM values in serum samples ranged from 34.73 to 2,156.19 mg/mL (by the new method). Deming regression analysis was performed to obtain slope, R^2, intercept and a scatter plot of data. Results are summarized in tables below.

CSF samples:

n	Slope (95% CI)	Y-Intercept (95% CI)	R^2
80	0.963 (0.946 to 0.980)	-0.133 (-0.190 to -0.076)	0.994

Serum samples:

n	Slope (95% CI)	Y-Intercept (95% CI)	R^2
80	1.048 (1.031 to 1.065)	5.695 (-12.7 to 24.117)	0.995

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The reference interval values of 429 to 1893 mg/L for serum IGMLC were established using a population of 130 apparently healthy male and female adults from California. The reference interval of 0.19 – 0.29 mg/L for CSF was taken from published literature [Burtis, C. A., Ashwood, E. R., Tietz, Texbook of Clinical Chemistry, 3rd Edition, W. B. Saunders, Philadelphia, PA (1999)].

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.