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

A. 510(k) Number:
k071002

B. Purpose for Submission:
Add indication for use for evaluation of cardiac disease on already cleared product- k010236

C. Measurand:
C-Reactive Protein

D. Type of Test:
Quantitative rate turbidimetry assay

E. Applicant:
Beckman Coulter Inc
.

F. Proprietary and Established Names:
Immage® Immunochemistry Systems High Sensitivity Cardiac C-Reactive Protein (CCRP)
CAL 5 Plus

G. Regulatory Information:

1. Regulation section:
   21CFR 866.5270
   21CFR 862.1150

2. Classification:
   Class II

3. Product code:
   NQD (Cardiac C-Reactive Protein, Antigen, Antiserum, and Control)
   JIX (Calibrator, Multi-analyte)

4. Panel:
   Immunology (82)
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See Indications for Use below.

2. Indication(s) for use:
   High Sensitivity Cardiac C-Reactive Protein (CCRP) reagent, when used in conjunction with IMMAGE® 800 Immunochemistry Systems and Calibrator 5

Plus, is intended for the quantitative determination of C-Reactive protein in human serum or plasma by rate nephelometry.

Clinical Significance: Measurement of C-Reactive protein (CRP) aids in evaluation of stress, trauma, infection, inflammation, surgery, and associated diseases. Cardiac CRP assays are indicated for use as an aid in the identification and stratification of individuals at risk for future cardiovascular disease. When used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, CRP may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndrome.

CAL 5 Plus (Calibrator 5 Plus), when used in conjunction with Beckman Coulter reagents, is intended for use on IMMAGE® Immunochemistry Systems for the calibration of Anti-Streptolysin O (ASO), C-Reactive Protein (CRP) and Rheumatoid Factor (RF).

3. Special conditions for use statement(s):
   For prescription use

4. Special instrument requirements:
   IMMAGE® 800 Immunochemistry System

I. Device Description:

High Sensitivity Cardiac C-Reactive Protein (CCRP) reagent is intended for the quantitative determination of C-Reactive protein in human serum or plasma by rate turbidimetry. The IMMAGE® 800 Immunochemistry Systems CCRP reagent is based on the highly sensitive Near Infrared Particle Immunoassay rate methodology. An anti-CRP antibody-coated particle binds to CRP in the patient sample resulting in the formation of insoluble aggregates causing turbidity. The rate of aggregate formation is directly proportional to the concentration of CRP in the sample.

CAL 5 Plus (Calibrator 5 Plus) is a frozen liquid serum matrix intended for use on IMMAGE® Immunochemistry Systems for the calibration of Anti-Streptolysin O (ASO), C-Reactive Protein (CRP) and Rheumatoid Factor (RF).

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Dade Behring CardioPhase High Sensitivity CRP

2. Predicate 510(k) number(s):
   k033908

3. Comparison with predicate:

	Similarities	
Immage Cardiac CCRP Reagent	Intended Use	Same as Behring CardioPhase hsCRP
	Use of Latex particle technology	Same as Dade Behring CardioPhase hsCRP and Immage CRPH
	Liquid stable reagent	The formulation is identical to Immage CRPH Reagent.
	Single point adjusted Calibration model	Same as IMMAGE CRPH Reagent
	Differences	
Immage Cardiac CCRP Reagent	Antibody source	IMMAGE CCRP uses goat and mouse while the Dade Behring Kit uses mouse only.
	Initial dilution range	The IMMAGE initial dilution range covers from 0.2 to 60.0 mg/L while the Dade Behring Kit covers from 3.0 to 220 mg/L
	Extended dilution range	The IMMAGE extended dilution range covers up to 1440.0 mg/L while the Dade Behring Kit covers the range from 0.16 to 16000.0 mg/L
	Calibration model	IMMAGE High Sensitivity Cardiac CCRP uses a different model equation for the predetermined calibration curve than IMMAGE CRPH.

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

1. CLSI Guideline, EP5-A2 Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline Second edition
2. CLSI Guideline, EP6-A Evaluation of the Linearity of Quantitative Analytical Methods; Approved Guideline
3. CLSI Guideline, EP9-A2 Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline Second edition
3. CLSI Guideline, EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation
3. CLSI Guideline, C28-A How to Define and Determine Reference Intervals in the Clinical Laboratory

L. Test Principle:

The IMMAGE® 800 Immunochemistry Systems CCRP reagent is based on the highly sensitive Near Infrared Particle Immunoassay rate methodology. An anti-CRP antibody-coated particle binds to CRP in the patient sample resulting in the formation of insoluble aggregates causing turbidity. The rate of aggregate formation is directly proportional to the concentration of CRP in the sample.

The chemical reaction scheme is as follows:

C-reactive protein (sample) + Particle bound anti-CRP (antibody)⇨
[C-reactive protein (sample)-antibody complex]

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Within-run and total imprecision studies were designed using CLSI EP5-A2 guideline. Three levels of serum based controls were run twice a day, in duplicate, for 20 days on the IMMAGE 800 System. Mean, SD, and % CV are calculated and shown in the tables below:

Within-run imprecision

Sample	N	Mean (mg/L)	SD (mg/L)	% CV
Level 1	80	0.807	0.0229	2.8
Level 2	80	13.56	0.4109	3.0
Level 3	80	51.538	1.7181	3.3

Total imprecision

Sample	N	Mean (mg/L)	SD (mg/L)	% CV
Level 1	80	0.807	0.0279	3.5
Level 2	80	13.56	0.4248	3.1
Level 3	80	51.538	2.1933	4.3

b. Linearity/assay reportable range:

i.) Linearity study was designed using the CLSI EP6-A guideline. Serial dilutions of high serum samples (ranging from 2.80 to 79.92 mg/L), a total of seven points, were used on the IMMAGE 800 System for this study. The linear regression of the correlation was as follow:

$y = 1.0114x + 0.2776$, $r^2 = 0.9992$

A low sample with concentration of 13.49 mg/L with serial dilutions (ranging from 0.17 to 13.39 mg/L), a total of seven points, was also tested to show the low end linearity and the linear regression was as follow:

$y = 1.0317x + 0.0794$, $r^2 = 0.9959$

The sponsor claimed the linearity range of 0.2 to 60.0 mg/L for the initial measuring range.

ii.) A dilution study was done to verify the extended range on the candidate device. Seventeen (48) serum samples with different CRP concentrations (ranging from 66.9

to 323 mg/L) were tested on the IMMAGE 800 System using the Immage® Immunochemistry Systems High Sensitivity Cardiac C-Reactive Protein (CCRP) and the predicate device. Linear regression showed y = 1.0595x + 2.726 with an r^2 = 0.9854. The sponsor will claim that the extended range is 0.2 to 144 mg/L.

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

The calibrator for this assay is traceable to the International Federation of Clinical Chemistry International Reference Preparation for Plasma Proteins lot CRM 470 certified by the Bureau of Reference of the European Community. Accelerated stability data supports a shelf-life/open vial claim for Beckman IMMAGE CAL 5 Plus of twenty-four (24) months. The sponsor's acceptance criterion is 100 ± 5% recovery of the target control. Each serum or plasma donor unit used in the preparation of this material was tested by United States Food and Drug Administration (FDA) approved methods and found to be negative for the antibodies to HIV and HCV and non-reactive for HBSAg.

d. Detection limit:

i.) An analytical sensitivity study was performed using several low standards and the IMMAGE 800 System. Analytical sensitivity is defined as the lowest measurable concentration which can be distinguished from zero with 95% confidence. The standards were run in 20 replicates and the mean and SD was calculated based on the observed results. The sponsor claimed that the analytical sensitivity of the candidate device is 0.06 mg/L.

ii.) A functional sensitivity study was performed using serum samples and the IMMAGE 800 System. The functional sensitivity is defined as the lowest concentration that can be measured with an inter-assay CV of 20%. Six serum samples with different CRP concentrations were run using 20 replicates of each level sample across two instruments (40 total replicates) and two lots of reagent, and the mean and SD were calculated based on the observed results. The sponsor claimed that the functional sensitivity of the candidate device is 0.11 mg/L.

e. Analytical specificity:

Interference testing was not repeated and remained unchanged compared to the previously cleared IMMAGE High Sensitivity CRP (k010236).

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were designed using CLSI EP9-A as a guideline and employed Deming regression analysis to analyze the data. The correlation test results

were obtained using the Dade Behring CardioPhase High Sensitivity CRP (predicate) on the BN System and the Immage® Immunochemistry Systems High Sensitivity Cardiac C-Reactive Protein (CCRP) (candidate) on the IMMAGE 800 System. 157 serum patient samples ranging from 0.2 to 60.0 mg/L were utilized for this study and no samples were diluted or fortified. The Deming regression correlation is as follows:

y = 0.965x + 0.334, r = 0.9962

A separate regression was calculated for samples ranging from 0.2 to 10 mg/L (cardiac range) and Deming regression correlation is as follows:

y = 1.013 – 0.026, r = 0.9939, N = 98.

(Y= candidate device, X = predicate device)

b. Matrix comparison:

Matrix comparison studies using 48 healthy individuals with paired serum, EDTA (1.5 mg/mL), Lithium Heparin (14 Units/mL), and Sodium Heparin (14 Units/mL) were analyzed using the Immage® Immunochemistry Systems High Sensitivity Cardiac C-Reactive Protein (CCRP) (candidate) on the IMMAGE 800 System. Samples ranged from 0.022 to 27.158 mg/L for EDTA and 0.022 to 27.148 mg/L for Li and Na Heparin. Deming regression analysis was used to evaluate the results.

For serum vs. Sodium heparin plasma: y = 1.011x - 0.026, r = 0.9996

For serum vs. Lithium heparin plasma: y = 1.024x - 0.058, r = 0.9987

For serum vs. EDTA plasma: y = 0.993x + 0.011, r = 0.9996

(X = serum results)

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):
Subject device showed comparable analytical performance in 510(k) submission k010236 and has provided updated performance information (method comparison) to the predicate device, CardioPhase High Sensitivity CRP, which.was used in the clinical studies supporting an indication for cardiovascular use.

4. Clinical cut-off:
Not Applicable

5. Expected values/Reference range:

i.) AHA/CDC* recommends the following cardiovascular disease risk assessment guidelines for CRP.

Risk Level	**CRP (mg/L)**
Low	< 1.0
Average	1.0 – 3.0
High	> 3.0

* Pearson,T.A, Mensag, G.A., Alexander RW, Anderson JL, Canon RO 3rd, Criqui M, Fadl YY., Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F, *Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A statement for Healthcare Professional From the Centers for Disease Control and Prevention and the American Heart Association Circulation.*107:499-511 (2003)

ii.) The reference range interval values for CRP were based on a population of 615 apparently healthy, non-smoking, ≥ 18 years of age, male and female adults from a Southern California blood bank. The expected normal range is < 7.44 mg/L in 95% of the population tested.

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.