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:
**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:
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®
Immunocchemistry 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:

\[ y = 0.965x + 0.334, \quad r = 0.9962 \]

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

\[ y = 1.013 - 0.026, \quad r = 0.9939, \quad N = 98. \]

\( (Y= \text{candidate device}, \quad X = \text{predicate device}) \)

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: \( y = 1.011x - 0.026, \quad r = 0.9996 \)

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

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

\( (X = \text{serum results}) \)

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.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Average</td>
<td>1.0 – 3.0</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 3.0</td>
</tr>
</tbody>
</table>


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.