

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

A. 510(k) Number:

k070626

B. Purpose for Submission:

Add indication for use for evaluation of cardiac disease on already cleared product- k010597

C. Measurand:

C-Reactive Protein

D. Type of Test:

Quantitative rate turbidimetry assay

E. Applicant:

Beckman Coulter Inc.

F. Proprietary and Established Names:

Synchron Systems High Sensitivity Cardiac C-Reactive Protein (CRPH) Reagent

G. Regulatory Information:

1. Regulation section:

21CFR 866.5270

2. Classification:

Class II

3. Product code:

NQD (Cardiac C-Reactive Protein, Antigen, Antiserum, and Control)

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

See Indications for Use below.

2. Indication(s) for use:

High Sensitivity Cardiac C-Reactive Protein (CRPH) Reagent, when used in conjunction with Synchron LX PRO System, UniCel DxC 600/800 System(s) and Synchron Systems CAL 5 Plus, is intended for the quantitative determination of C-Reactive protein (CRP) in human serum or plasma by rate turbidimetry.

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.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

Synchron LX PRO System and UniCel DxC 600/800 System(s).

I. Device Description:

Each kit contains the following items: Two CRPH reagent cartridges (2x200 tests) and one lot-specific parameter card.

Reagent constituents:

- CRP Antibody (particle bound goat and mouse anti-CRP antibody) – 17.3 mL in compartment B
- Reagent buffer – 47.8 mL in compartment A
- Sodium Azide (used as a preservative) - < 0.1% (w/w)
- Bovine Serum Albumin – 0.125% (w/v)
- Other non-reactive chemicals necessary for optimal system performance

J. Substantial Equivalence Information:

1. Predicate device name(s):

Dade Behring CardioPhase High Sensitivity CRP and Synchron Systems High Sensitivity CRPH Reagent

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

k033908, k010597

3. Comparison with predicate:

Similarities and Differences between candidate device and Dade Behring CardioPhase High Sensitivity CRP (Predicate device)-k033908		
Item	Synchron Systems High Sensitivity Cardiac CRPH (Candidate device)	Dade Behring CardioPhase High Sensitivity CRP (Predicate device)
Indications for Use	Measurement of C-Reactive protein (CRP) aids in evaluation of stress, trauma, infection, 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 syndrome, CRP may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndrome.	Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. Measurements may also be used as an aid in the identification of individuals at risk for future cardiovascular disease. High sensitivity CRP (hsCRP) measurements when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndromes.
Instruments	Synchron LX PRO System and UniCel DxC 600/800 System(s).	Dade Behring BN Systems
Assay Type	Particle enhanced immunonephelometry	Particle enhanced immunonephelometry
Antibodies	Particle bound Anti-CRP antibody; goat and mouse antibodies	Particle bound Anti-CRP antibody; mouse
Expected Values	< 7.48 mg/L in 95% of the population tested. The expected value is based on a population of 551 apparently healthy adults in Southern California.	Expected values for healthy individuals as noted in the literature is <3 mg/L. The normal range of CRP in the serum of 2147 apparently healthy individuals using the CardioPhase hsCRP Assay was found to be 90% 1.69 mg/L 95% 2.87 mg/L As CRP is a nonspecific indicator for a wide range of disease processes, and as the reference individuals are affected by many factors that may differ for each population studied, each laboratory should determine its own reference interval.
Reference standards	CRM 470	CRM 470

Measuring Range	0.2 to 80.0 mg/L	0.175 to 1100 mg/L
Analytical Sensitivity	0.11 mg/L	0.175 mg/L
Functional Sensitivity	0.18 mg/L	Not reported in the package insert
Sample Type	Serum, heparinized and EDTA plasma	Serum, heparinized, and EDTA plasma
Interferences	No significant interference from bilirubin (up to 30 mg/dL), hemoglobin (up to 650 mg/dL), triglycerides (up to 700 mg/dL), or RF (up to 300 IU/mL). Lipemic or turbid samples should not be used with this assay	No significant interference from bilirubin (up to 600 mg/L), hemoglobin (up to 10 g/L) or triglycerides (up to 16 g/L). Lipid or turbid samples should not be used. HAMA may cause an inaccurate result.
Calibration Interval	Recommended 30 days calibration interval	Reference curve valid for 4 weeks and beyond as indicated by control results

Similarities and Differences between candidate device and Synchron Systems High Sensitivity CRPH (predicate device)- k010597		
Item	Synchron Systems High Sensitivity Cardiac CRPH (Candidate device)	Synchron Systems High Sensitivity CRPH (Predicate device)
Indications for Use	Cardiac risk assessment and injury/inflammation	Injury/inflammation
Assay Type	Particle enhanced immunonephelometry	same
Antibodies	Particle bound Anti-CRP antibody; goat and mouse antibodies	same
Expected Values	< 7.48 mg/L	same
Reference standards	CRM 470	same
Measuring Range	0.2 to 80.0 mg/L	same
Extended Range	60.0 to 380.0 mg/dL	same
Analytic Sensitivity	0.11 mg/L	same
Functional Sensitivity	0.18 mg/L	same
Sample Type	Serum, heparinized and EDTA plasma	same
Sample size	10 µL	20 µL

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*

L. Test Principle:

Synchron Ssystems High Sensitivity Cardiac CRP 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 chemical reaction scheme is as follows:

C-reactive protein (sample) + Particle bound anti-CRP (antibody) \Rightarrow
[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 UniCel DxC 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	0.630	0.019	3.1
Level 2	80	13.68	0.222	1.6
Level 3	80	56.39	0.907	1.6

Total imprecision

Sample	N	Mean (mg/L)	SD (mg/L)	% CV
Level 1	80	0.630	0.033	5.3
Level 2	80	13.68	0.381	2.8
Level 3	80	56.39	1.823	3.2

b. Linearity/assay reportable range:

- i.) The linearity study was designed using the CLSI EP6-A guideline. Serial dilutions of high serum samples were used on the Synchron LX20 PRO system for this study.

The linear regression of the correlation was as follows:

$$Y = 1.0051 X + 0.1415, r^2 = 0.9977$$

A low sample with concentration of 13.6 mg/L with serial dilutions was also tested to show the low end linearity and the linear regression was as follows:

$$Y = 0.9861 X + 0.0941, r^2 = 0.9993$$

The sponsor claimed a linear range of 0.2 to 80.0 mg/L.

ii.) A dilution study was done to verify the extended range on the candidate device. Seventeen (17) serum samples with different CRP concentrations were tested on the Synchron LX20 PRO system using the Synchron Systems Cardiac High Sensitivity CRPH Reagent (candidate) and the Synchron Systems High Sensitivity CRPH Reagent (predicate). The results demonstrated that the two assays agreed within $\pm 15\%$. The sponsor claimed that the extended (ORDAC) range is 60.0 to 380.0 mg/L.

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

Synchron Systems Cardiac High Sensitivity CRPH Reagent is traceable to CRM 470 reference materials.

d. Detection limit:

i.) An analytical sensitivity (limit of blank) study was performed using several low standards and the Synchron LX 20 PRO System. Analytical sensitivity was 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 0.11 mg/L.

ii.) A functional sensitivity (limit of quantitation) study was performed using serum samples and the UniCel DxC System. The functional sensitivity was 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 in duplicates of 10 and the mean and SD were calculated based on the observed results. The sponsor claimed that the functional sensitivity of the candidate device is 0.18mg/L.

e. Analytical specificity:

Interference testing was not repeated and remained unchanged as the previously cleared predicate device, Synchron Systems High Sensitivity CRP (k010597)

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 Synchron System High Sensitivity Cardiac CRPH reagent (candidate) on the UniCel DxC System. 269 serum patient samples ranging from 0.2 to 80.0 mg/L were utilized for this study and no samples were diluted or fortified. The Deming regression correlation is as follows:

$$Y = 1.048 X + 0.024, r = 0.9899$$

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

$$Y = 1.030 - 0.008, r = 0.9910, N = 149.$$

(Y = candidate device, X = predicate device)

b. Matrix comparison:

Matrix comparison studies using 47 healthy individuals with paired serum, EDTA, Lithium Heparin and Sodium Heparin were analyzed using the Synchron System High Sensitivity Cardiac CRPH reagent (candidate) on the Synchron LX 20 PRO System. Samples ranged from 0.221 to 23.9 mg/L. Deming regression analysis was used to evaluate the results.

For serum vs Sodium heparin plasma: $Y = 0.984 X + 0.049, r = 0.9997$

For serum vs Lithium heparin plasma: $Y = 1.017X - 0.012, r = 0.9998$

For serum vs EDTA plasma: $Y = 0.982 X + 0.021, r = 0.9999$

(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):

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 551 apparently healthy, non-smoking, ≥ 18 years of age, male and female adults from a Southern California blood bank. The expected normal range is < 7.48 mg/L in 95% of the population tested. (See k010597).

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.