

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

**A. 510(k) Number:**

k060369

**B. Purpose for Submission:**

New device

**C. Measurand:**

C-Reactive Protein (CRP)

**D. Type of Test:**

Two-site sandwich immunoassay, quantitative

**E. Applicant:**

Dade Behring Inc.

**F. Proprietary and Established Names:**

Stratus® CS Acute Care™ CardioPhase® hsCRP TestPak (CCRP TestPak)

Stratus® CS Acute Care™ CardioPhase® hsCRP CalPak (CCRP CalPak)

Stratus® CS Acute Care™ CardioPhase® hsCRP DilPak (CCRP DilPak)

**G. Regulatory Information:**

1. Regulation section:

21 CFR 866.5270, C-reactive protein immunological test system

21 CFR 862.1150, Calibrator

2. Classification:

Class II

3. Product code:

NQD (cardiac c-reactive protein, antigen, antiserum, and control)

JIT (calibrator, secondary)

4. Panel:

Immunology (81) and Chemistry (75)

**H. Intended Use:**

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

**The Stratus CS Acute Care CardioPhase hsCRP TestPak:**

The Stratus CS Acute Care CardioPhase hsCRP assay is an in vitro diagnostic reagent for the quantitative determination of C-reactive protein (CRP) in lithium and sodium heparin plasma. In acute phase response, increased levels of a number of plasma proteins, including C-reactive protein, is observed. Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. High sensitivity CRP (hsCRP) measurements may be used as an independent risk marker for the identification of individuals at risk for future cardiovascular disease. Measurements of hsCRP, when used in conjunction with traditional 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.

**The Status CS Acute Care CardioPhase hsCRP CalPak:**

The Status CS Acute Care CardioPhase hsCRP calibrator is an in vitro diagnostic product intended to be used for the calibration of the Acute Care CardioPhase method on the Stratus CS analyzer.

**The Status CS Acute Care CardioPhase hsCRP DilPak:**

The Stratus CS Acute Care CardioPhase hsCRP Dilution Pak is an in vitro diagnostic product intended to be used in conjunction with the Acute Care CardioPhase hsCRP Test Pack for measurement of samples with elevated levels of C-reactive protein.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

Dade Behring Stratus CS Analyzer

**I. Device Description:**

The Stratus CS Acute Care CardioPhase hsCRP TestPak is required to perform the CRP test. Each box contains 60 TestPaks and each TestPak is comprised of individual wells containing the following reagents: alkaline phosphatase conjugated anti-CRP mouse monoclonal antibody, dendrimer linked anti-CRP mouse monoclonal antibody, 4-methylumbelliferyl phosphate in a diethanolamine buffer with preservative.

The Stratus CS Acute Care CardioPhase hsCRP CalPak contains native CRP in a human serum matrix with a preservative. It is a single-use product made up of three wells with a defined concentration of CRP calibrator. Each box of CalPak contains enough reagent for five (5) calibrations.

The Stratus CS Acute Care CardioPhase hsCRP DilPak contains a liquid buffered human protein matrix with stabilizers and preservative. Each box of DilPak contains enough reagent for five (5) dilutions.

Human source material used in the CalPak and DilPak was tested and found negative for HIV-1/2, HBsAg, and HCV by FDA-approved methods.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):  
Dade Behring CardioPhase hsCRP
2. Predicate 510(k) number(s):  
k033908
3. Comparison with predicate:

<b>Similarities</b>		
Item	Device	Predicate
Standardization	Same	Traceable to IFCC/BCR/CAP CRM 470

<b>Differences</b>		
Item	Device	Predicate
Assay type and analyzer	Based on Radial Partition Immunoassay (RPIA) technology on the Stratus CS system	Particle enhanced immunonephelometry on the BN system
Sample type	Lithium and sodium heparin plasma	Serum, heparin plasma, EDTA plasma
Reportable range	0.1 to 50 mg/L	0.18 to 200 mg/L
Limit of Quantitation (Functional Sensitivity)	≤ 0.2 mg/L	Not specified

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

Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition (CLSI EP7-A2)

Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition (CLSI EP5-A2)

Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Second Addition (CLSI EP9-A2)

Guidance for Industry and FDA Staff, Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays.

**L. Test Principle:**

The Stratus CS Acute Care CardioPhase hsCRP method is a two-site sandwich assay based upon solid phase Radial Partition Immunoassay (RPIA) technology. In this procedure, dendrimer linked monoclonal antibody is added to the center portion of a square piece of glass fiber paper in the CCRP TestPak. This antibody recognizes a distinct antigenic site on the CRP molecule. Sample is then added onto the paper where it reacts with the immobilized antibody. After a short incubation, a conjugate consisting of enzyme-labeled monoclonal antibody directed against the same antigenic site is pipetted onto the reaction zone of the paper. During this second incubation period, enzyme-labeled antibody reacts with the bound CRP, forming an antibody-antigen-labeled antibody sandwich. The unbound labeled antibody is later eluted from the field of view of the Stratus CS analyzer by applying a substrate wash solution to the center of the reaction zone. By including substrate for the enzyme within the wash solution, initiation of enzyme activity occurs simultaneously with the wash. The enzymatic rate of the bound fraction increases directly with the concentration of CRP in the sample. The reaction rate can then be measured by an optical system that monitors the reaction rate via front surface fluorescence. All data analysis functions are performed by the microprocessor within the analyzer.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

a. *Precision/Reproducibility:*

The precision study was performed using a protocol similar to CLSI EP5-A2 and included commercial controls, human sera with elevated CRP and a patient pool spiked with CRP. Specimens at each concentration (1.16, 2.28, 3.32, 16.59, and 39.3 mg/L) were analyzed twice a day for 20 days.

Repeatability ranged from 2.34-3.24% CV and within lab imprecision ranged from 3.01-4.75% CV.

Limit of Quantitation (Functional Sensitivity) was evaluated by determining the total imprecision of samples with very low concentrations of analyte. Three samples were tested in duplicate once per day for 20 days with one lot of reagents on two Stratus CS analyzers. The limit of quantitation corresponds to a coefficient of variation (CV) of 10% at a CRP concentration  $\leq 0.2$  mg/L.

b. *Linearity/assay reportable range:*

The assay range is 0.1 to 50 mg/L. An error code “High Fluorescence Error” will be displayed for samples exceeding the upper end of the reportable range. Linearity was evaluated by comparing the observed versus expected values obtained with the Stratus CS Acute Care CardioPhase hsCRP method across the range of the assay. Three samples were tested in all. Two plasma samples with elevated concentrations of CRP (10 and 20 mg/L) were mixed with normal plasma with low CRP in different proportions. A third sample with CRP concentration 45 mg/L was mixed with saline buffer using a similar protocol. The observed results were within  $\pm 10\%$  of the expected results for the samples tested.

High dose hook effect was evaluated by testing normal human plasma spiked with CRP at high concentrations exceeding the upper range of the assay (50 mg/L). No hook effect was seen with samples with CRP concentration up to 2000 mg/L.

Accurate dilution was demonstrated for samples greater than 50 mg/L using the Stratus CS Acute Care CardioPhase hsCRP DilPak and the 1:5 automated dilution feature. Users are advised to manually dilute samples 1:10 with normal saline if the concentration still exceeds the upper range using the 1:5 automated dilution (samples greater than 250 mg/L).

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

**Traceability and Value Assignment:**

The Stratus CS Acute Care CardioPhase hsCRP CalPak is traceable to reference material CRM 470 in the following value assignment scheme. First a six-level heparin plasma anchor pool is established using patient samples at CRP levels across the assay range. The anchor pool samples are assayed using the predicate device (CardioPhase hsCRP on the BN II system) which was standardized to the CRM 470. A “master pool” consisting of one calibration point with CRP concentration of  $\sim 40$  mg/L is prepared from native CRP patient serum, standardized using the anchor pool. The Stratus CS Acute Care CardioPhase hsCRP CalPak also has a concentration  $\sim 40$  mg/L and is compared to the master pool to ensure lot to lot consistency. Additionally the CRM 470 reference material is assayed using the Stratus CS Acute Care CardioPhase hsCRP method and is monitored over time to ensure recovery within  $\pm 10\%$  of the target.

**Stability:**

The sponsor provided real-time and accelerated stability testing protocols and acceptance criteria. Real time studies to support the shelf-life of the Stratus CS Acute Care CardioPhase hsCRP TestPak, CalPak, and DilPak are ongoing. The labeling states that the Stratus CS Acute Care CardioPhase hsCRP TestPak, CalPak, and DilPak are stable until the expiration date printed on

each box label when stored at 2-8°C. TestPaks, CalPaks and DilPaks are designed to be used only once.

*d. Detection limit:*

The Analytical Sensitivity was defined as the concentration that corresponds to two standard deviations above the mean of a sample containing no CRP. Twenty replicates of a protein-matrix calibrator (0 mg/L) were evaluated with the assay and resulted in an analytical sensitivity of ~0.05 mg/L. The product labeling claims an analytical sensitivity of  $\leq 0.10$  mg/L

*e. Analytical specificity:*

The potential for interference from endogenous and exogenous substances on the assay was evaluated by spiking plasma containing approximately 3 mg/L CRP with the appropriate concentration of the test substance and comparing the recovery of the test sample to that of a control sample. A difference in recovery between the test sample and control sample exceeding 10% was considered interference by the sponsor.

Hemoglobin (up to 1000 mg/dL), conjugated and unconjugated bilirubin (up to 60 mg/dL), lipid (up to 3000 mg/dL), cholesterol (up to 500 mg/dL), and IgM (9 g/L) did not interfere with the test. Results for a panel of other substances tested, including over-the-counter and prescription drugs, can be found in the package insert.

*f. Assay cut-off:*

Not applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

A method comparison study was performed with heparin plasma patient samples (n=154). The regression analysis was performed using the Passing-Bablok model equation. A summary of the results are in the table below.

<b>Comparative Method</b>	<b>Range of Sample values</b>	<b>Slope</b>	<b>Intercept</b>	<b>Correlation Coefficient</b>	<b>N</b>
Dade Behring <i>CardioPhase</i> ® hsCRP, performed on the BN™ System	0 – 50 mg/L	0.952	0.098	0.999	154
	0 – 10 mg/L	0.997	0.047	0.995	123
	0 – 5 mg/L	1.002	0.042	0.994	107

b. *Matrix comparison:*

In order to demonstrate equivalent results between lithium heparinized and sodium heparinized plasma, a split sample comparison was performed (n=35). A linear regression analysis yielded the following results for samples ranging from ~0.2 to 23 mg/L:  $y = 1.00x + 0.007$  ( $r = 0.999$ ).

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:

Relative risk categories and average hsCRP levels as recommended in the AHA/CDC Scientific Statement are found in the labeling:

<b>Risk</b>	<b>hsCRP (mg/L)</b>
Low	< 1.0
Average	1.0 - 3.0
High	> 3.0

**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.