

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

A. 510(k) Number:

k053109

B. Purpose for Submission:

New device for premarket clearance

C. Measurand:

C-Reactive Protein

D. Type of Test:

Quantitative / One step enzyme immunoassay

E. Applicant:

DADE BEHRING, INC.

F. Proprietary and Established Names:

DIMENSION CARDIOPHASE HIGH SENSITIVITY CRP FLEX REAGENT
CARTRIDGE

G. Regulatory Information:

| Product Code | Classification | Regulation Section | Panel |
|--|-----------------------|---|---------------------------|
| <u>Cardiac C-reactive protein, antigen, antiserum, and control (NQD)</u> | <u>Class II</u> | <u>21 CFR 866.5270, C-reactive protein immunological test system.</u> | <u>82 IMMUNOLOGY (IM)</u> |

H. Intended Use:

1. Intended use(s):

The Dimension® CardioPhase® high sensitivity C-reactive protein method for the Dimension® clinical chemistry system with the heterogeneous immunoassay module is an in vitro diagnostic test intended to quantitatively measure C-reactive protein levels in human serum and heparinized plasma.

2. Indication(s) for use:

The Dimension® **CardioPhase**® high sensitivity C-reactive protein (CCRP) method for the Dimension® clinical chemistry system with the heterogeneous immunoassay module is an in vitro diagnostic test intended to quantitatively measure C-reactive protein levels in human serum and heparinized 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 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.

3. Special conditions for use statement(s):

Prescription

4. Special instrument requirements:

The Dimension® **CardioPhase**® high sensitivity C-reactive protein method requires one of the following instruments: the Dade Behring Dimension® RxL clinical chemistry system (K944093), the Dade Behring Dimension® RxL Max clinical chemistry system (K 944093), the Dade Behring Dimension® Xpand clinical chemistry system (K010061) or the Dade Behring Dimension® Xpand PLUS clinical chemistry system (K010061). All require the heterogeneous module.

I. Device Description:

The Dimension® CardioPhase® high sensitivity CRP Flex® reagent cartridge (CCRP- RF434) is an in vitro diagnostic device that consists of prepackaged reagents in a plastic eight well cartridge for use on the Dade Behring Dimension® clinical chemistry system for the quantitative determination of C-reactive protein in human serum and plasma.

J. Substantial Equivalence Information:

| Predicate | Item | Similarities | Differences |
|---|-------------------------------------|--|--|
| K033908 hsCRP Reagent for the BN systems | Intended Use | Both are invitro diagnostic reagent forthe quantitative determination of C-reactive protein. | |
| K033908 hsCRP Reagent for the BN systems | Sample Types | Both are for serum and heparinized plasma. | |
| K033908 hsCRP Reagent for the BN systems | Standardization | Both are traceable to CRM 470 | |
| K033908 hsCRP Reagent for the BN systems | Reagents | | New device uses chromium dioxide particles and a β -galactosidase conjugate reagent; each coated with a monoclonal antibody specific for the C-reactive protein molecule. Predicate device uses polystyrene particles coated with monoclonal antibodies specific to human CRP. |
| K033908 hsCRP Reagent for the BN systems | Principle | | New device uses the one step enzyme immunoassay based on the "sandwich"principle. The predicate device uses the immunochemical principle in which the intensity of scattered light is proportional to the concentration of analyte in the sample. |
| K033908 hsCRP Reagent for the BN systems | Wavelength | | The new device uses the 405nm and 510nm wavelengths. The predicate device uses the 840nm wavelength. |
| K033908 hsCRP Reagent for the BN systems | Measurement Type | | The new device uses photometry. The predicate device uses nephelometry. |
| K033908 hsCRP Reagent for the BN systems | Analytical Measurement Range | | The AMR of the new devices is 0.10 to 25.0 mg/L. The AMR of the predicate device is 0.16 to 10.0 mg/L. |
| K033908 hsCRP Reagent for the BN systems | Extended Clinical Measurement Range | | The new device can achieve an extended assay range of 25 to 150 mg/L through auto-dilute. The predicate device can achieve an extended assay range of 3.1 to 200 mg/L through an alternative assay protocol. |

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

| STANDARDS |
|--|
| Title and Reference Number |
| Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A) |
| Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A) |
| Continuous Quality Improvement: Essential Management Approaches; Approved Guideline (GP 22-A) |
| Stability Testing of In Vitro Diagnostic Reagents (13640) |
| Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2) |
| Medical devices - Application of risk management to medical devices (14971:2000) |
| Medical Devices - Symbols to be used with medical device labels, labeling and information to be supplied (15223) |

Other Standards

| GUIDANCE | | | |
|--|--------|----------|---|
| Document Title | Office | Division | Web Page |
| Guidance for Industry and FDA Staff - Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use | | | http://www.fda.gov/cdrh/ocd/guidance/4444.html |
| Guidance for Industry - Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays | OIVD | DCTD | http://www.fda.gov/cdrh/oivd/guidance/1246.html |

L. Test Principle:

The CCRP method is a one step enzyme immunoassay based on the “sandwich” principle. Sample is incubated with chromium dioxide particles and a β -galactosidase conjugate reagent; each coated with a monoclonal antibody specific for the C-reactive protein molecule. A chrome particle/C-reactive protein/conjugate sandwich forms during the incubation period. Unbound conjugate is removed by magnetic separation and washing. After separation and washing, the particle/ C-reactive protein /conjugate sandwich is transferred to the cuvette where the sandwich bound β -galactosidase is combined with the chromogenic substrate o-nitrophenyl-beta-D-galactopyranoside (ONPG). β -galactosidase catalyzes the hydrolysis of ONPG to o-nitrophenol (ONP).

The change in absorbance due to the formation of ONP is directly proportional to the concentration of C-reactive protein present in the patient sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility testing was done in accordance with the CLSI/NCCLS (EP5-A2) Approved Guideline for Evaluation of Precision Performance of Clinical Chemistry Devices. Commercial controls and human serum and plasma pools were analyzed in duplicate, once a day, for 20 days. The within-run (repeatability) and total (within-lab) standard deviations were calculated by analysis of variance (ANOVA) method. Commercially available Bio-Rad Liquichek® Lipid Controls were used. Human serum and plasma pools prepared and aliquoted by Dade Behring Inc. were used.

| Reproducibility | | | |
|-----------------|-------|--------------------------|------------|
| Material | mg/L | Standard Deviation (%CV) | |
| | | Repeatability | Within-Lab |
| Serum pool 1 | 3.07 | 0.05 (1.5) | 0.07 (2.4) |
| Serum pool 2 | 10.83 | 0.14 (1.3) | 0.18 (1.7) |
| Plasma pool 1 | 11.15 | 0.18 (1.7) | 0.21 (1.9) |
| Control 1 | 0.84 | 0.02 (2.9) | 0.05 (5.6) |
| Control 2 | 4.40 | 0.07 (1.6) | 0.11 (2.4) |

b. *Linearity/assay reportable range:*

Linearity across the assay range was confirmed by testing mixtures of a high and low sample. Observed CRP values were plotted vs expected CRP values. A linear regression analysis was performed on the data and plotted. The observed linearity across the reportable range has a correlation coefficient of 0.997, slope of 0.989 and an intercept of -0.686. The Dimension® CCRP assay is linear across the claimed assay range claim of 0.0 mg/L to 15.0 mg/L.

To test recovery, an experiment was performed using the following protocol. Known amounts of CRP were added to human serum and plasma samples. CCRP concentrations on these samples were then measured and the calculated percent recovery ranged from 101% to 105%.

CRP results greater than 15 mg/L will generate an “Above Assay Range” test result message. According to the CCRP Instructions for Use, readings in excess of 15 mg/L may be repeated after diluting the sample with Purified Water to produce a sample concentration within the assay range. The resulting readout will then be multiplied by the dilution factor entered into the system to give the concentration of the undiluted sample. The Dimension®

instrument also has the capability to “auto dilute” samples above the assay range by re-sampling with a reduced sample volume (2 µL) resulting in a 1:6 dilution of the sample.

A parallelism experiment was performed to demonstrate the ability of the method to show a consistent linear dilution profile between its calibrator and test specimens.

The possibility of hook effect occurring when using the Dimension® CCRP assay was evaluated with samples above the assay range that ranged from 400 to 2500 mg/L. See the attached document entitled "Hook Effect".

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

The recommended reference material for the Dimension® CCRP method is the Dimension® CCRP Calibrator (Cat. No. RC434). The assigned values of this product are standardized to the International Federation of Clinical Chemistry (IFCC) International Reference Preparation for Plasma Proteins, the Community Bureau of Reference (BCR) and the College of American Pathologists (CAP). The basis of this international standardization is the IFCC/BCR/CAP reference preparation for 14 human serum proteins (Lot No. 91/0619=CRM470=RPPHS 91/0619) (lot V).

Subject of k053104

d. Detection limit:

The analytical sensitivity of the Dimension® CCRP method is 0.10 mg/L . The analytical sensitivity is defined as the mean value (n=20) plus two standard deviations of the low level 1(0mg/L)CCRP Calibrator. The Lower Limit of Quantification (LoQ) or functional sensitivity of the Dimension® CCRP method is 0.17mg/L. The functional sensitivity represents the lowest concentration with an observed 10% coefficient of variation.

e. Analytical specificity:

Interference testing was performed according to the CLSI/NCCLS Protocol EP-7A. A summary of the substances that do not interfere with the Dimension® CCRP method when present in serum at the concentrations indicated can be found in the package insert. Inaccuracies (biases) due to these substances are less than 10% at a CRP level equivalent to 3.0 mg/L/mL.

f. Assay cut-off:

The AHA/CDC Scientific Statement provides the following risk assessment guidelines:

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

Submission includes a bibliography reference to support cardiac risk assessment cutoffs/guidelines. No studies were done as part of this submission.

Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998; 97:2007-11.

2. Comparison studies:

a. *Method comparison with predicate device:*

Samples were collected, handled and stored according to the recommendations in the package insert sheet. All samples were individual native serum or Li/Na plasma samples. Method Comparison studies were performed at the following two external clinical sites:

University of Maryland, School of Medicine (UMMC) = Site 1, This site had one operator with a medical technology background and was trained at the Dade Behring Customer Training Center.

Methodist Medical Center of Illinois (MMCI) = Site 2. This site had one operator with a medical technology background and was trained at the Dade Behring Customer Training Center.

Laboratory personnel such as medical technologist and medical technicians represent the intended user for this device.

Linear Regression Statistics:

Dimension® CardioPhase® hsCRP method vs. CardioPhase® hsCRP on the BN systems 0-15 mg/L

| Site | Slope | Y Intercept | r | Sy,x | n | Range (mg/L) |
|-------------|-------|-------------|-------|------|-----|--------------|
| BN ProSpec® | 0.96 | 0.25 | 0.998 | 0.23 | 115 | 0.19 – 13.88 |
| BN™ II | 1.01 | 0.07 | 0.997 | 0.29 | 132 | 0.19 – 14.96 |

Dimension® CardioPhase® hsCRP method vs. CardioPhase® hsCRP on the BN systems 0-10 mg/L

| Site | Slope | Y Intercept | r | Sy,x | n | Range (mg/L) |
|-------------|-------|-------------|-------|------|-----|--------------|
| BN ProSpec® | 1.00 | 0.16 | 0.997 | 0.18 | 105 | 0.19 – 9.52 |
| BN™ II | 1.04 | -0.02 | 0.996 | 0.21 | 120 | 0.19 – 9.79 |

b. Matrix comparison:

Serum vs. Plasma Comparison

Serum, lithium heparinized or sodium heparinized plasma are the recommended specimens for the Dimension® CCRP assay. A split sample comparison was performed at Glasgow Research Laboratory. Fifty-five samples were drawn and run randomly on the Dimension® RxL clinical chemistry system.

Matched specimens of serum and heparinized plasma were drawn from volunteers and processed by the CCRP method on the Dimension®. Linear regression analysis showed excellent agreement between serum, lithium heparin plasma and sodium heparin plasma specimens.

| Serum verses | Slope | Y Intercept | r | n |
|-----------------|-------|-------------|------|----|
| Lithium Heparin | 1.03 | -0.17 | 0.99 | 55 |
| Sodium Heparin | 1.01 | -0.10 | 1.00 | 55 |

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 Dimension® CardioPhase® (CCRP) assay has similar imprecision, known interferences, comparable calibrators, and similar intended uses to the predicate device, the CardioPhase® CRP Reagent for the BN® systems. The Dimension® CardioPhase® (CCRP) Flex® reagent cartridge has the following statements regarding reference intervals in the package insert.

Expected values for healthy individuals as noted in the literature are typically ≤ 3 mg/L. As CRP is a nonspecific indicator for a wide range of disease processes, and as the reference intervals are affected by many factors that may differ for each population studied, each laboratory should determine its own reference interval for CCRP as performed on the Dimension® clinical chemistry system.

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.