

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

A. 510(k) Number:

k061802

B. Purpose for Submission:

New device

C. Measurand:

C-Reactive Protein

D. Type of Test:

Quantitative Immuno-nephelometric

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Dimension Vista Cardiophase hsCRP Flex Reagent Cartridge, Protein 2 Calibrator, hsCRP Control Low, HsCRP Control H

G. Regulatory Information:

1. Regulation section:

21 CFR§-866.5270 C-reactive protein immunological test system

21 CFR§-862.1150 Calibrator

21 CFR§-862.1660- Quality control material

2. Classification:

Class II, II and I, respectively

3. Product code:

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

JIX-Calibrator, Multi-Analyte Mixture

JJY – Multi-Analyte Controls

4. Panel:

Immunology (81) Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

Dimension Vista™ CardioPhase® hsCRP Flex® reagent cartridge:

The CardioPhase® hsCRP method is an in vitro diagnostic test for the quantitative measurement of C-reactive protein (CRP) in human serum and plasma by means of particle enhanced immunonephelometry on the Dimension Vista™ System. High sensitivity CRP measurements may be used for evaluation of conditions thought to be associated with inflammation, in otherwise healthy individuals and as an independent risk marker for the identification and stratification 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.

Dimension Vista™ Protein 2 Calibrator:

Protein 2 Calibrator is an in vitro diagnostic product for the calibration of the high sensitivity C-reactive protein (hsCRP) method on the Dimension Vista™ System.

Dimension Vista™ high sensitivity CRP Control L and Dimension Vista™ high sensitivity CRP Control H:

hsCRP Control L and H are for use as assayed intralaboratory quality controls for the assessment of precision and analytical bias in determination of C-reactive protein (CRP) on the Dimension Vista™ System.

3. Special conditions for use statement(s):

AHA/CDC Expert Panel Recommendations¹:

The AHA/CDC Expert Panel has the following recommendations for limitations on the use of hsCRP:

- hsCRP levels should not be substituted for assessment of traditional cardiovascular risk factors.
- Application of management guidelines for acute coronary syndromes should not be dependent on hsCRP levels.
- When using the assay for risk assessment, patients with persistently unexplained, marked elevation of hsCRP (>10 mg/L) after repeated testing should be evaluated for non-cardiovascular etiologies.
- The expert panel recommends against screening of the entire adult population for hsCRP as a public health measure.
- Patients with evidence of active infection, systemic inflammatory processes or trauma should not be tested for cardiovascular disease risk assessment until these conditions have abated.
- Application of secondary prevention measures should not depend on

¹ Pearson TA, Mensah GA, Alexander RW, et al. Markers of Inflammation and Cardiovascular Disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499-511.

hsCRP determination, but rather an array of risk factors (global risk assessment).

- Serial measurements of hsCRP should not be used to monitor effects of treatment.
- Two separate hsCRP measurements (optimally two weeks apart) should be obtained before performing risk assessment, due to within-subject hsCRP variability.

4. Special instrument requirements:
Dade Behring Dimension Vista™ Analyzer

I. Device Description:

Reagents are in the following cassette format:

Wells	Form	Ingredient	Concentration	Source
1-8	Liquid	hsCRP Supplement Reagent: Phosphate buffer Polidocanol	1.9 g/L	
9-12	Liquid	High sensitivity CRP Reagent: Polystyrene particles Monoclonal antibodies	1 g/L 13 mg/L	Mouse

PROT2 CAL is a liquid, human serum based product containing C-reactive protein.
hsCRP CON L &H are liquid, human serum based product containing C-reactive protein.

Each donor used in the preparation of the control and calibrator material was tested by FDA approved methods for the presence of antibodies to HIV-1, HIV-2, HCV as well as surface antigen for HBV and found to be negative.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Dade Behring CardioPhase® hsCRP assay, N Rheumatology Standard SL and N/T Rheumatology Control SL
2. Predicate 510(k) number(s):
k033908, k964527, k962373
3. Comparison with predicate:

Feature	Dade Behring CardioPhase® hsCRP Assay	Dimension Vista™ CardioPhase® hsCRP Assay
1. Intended Use:	Same	Same

Feature	Dade Behring CardioPhase® hsCRP Assay	Dimension Vista™ CardioPhase® hsCRP Assay
2. Principle:	Same	Same
3. Standardization:	Same	Same
4. Antibody:	Same	Same
5. Reportable Range:	0.16 – 200 mg/L	0.16 – 9.5 mg/L
6. Calibrator:	N Rheumatology Standard SL	Dimension Vista™ Protein 2 Calibrator
Form:	Liquid, human serum	Liquid, human serum
Constituents:	RF, ASL and CRP	CRP
Traceable to:	ERM® -DA470 (known as CRM 470)	ERM® -DA470 (known as CRM 470)
Levels:	1	1
7. Control:	N/T Rheumatology Control SL 1/2	Dimension Vista™ high sensitivity CRP Control L and H
Form:	Liquid, human serum	Liquid, human serum
Constituents:	RF, ASL and CRP	CRP
Traceable to:	International Reference Preparation – RF and ASL CRM 470 - CRP	CRM 470
Levels	Low and High	Low and High
8. Analyzer:	BN™ Systems	Dimension Vista™ System

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

CLSI - Evaluation of Precision Performance of Clinical Chemistry Devices - EP05-A2
 CLSI - Interference Testing in Clinical Chemistry - EP07-A2

L. Test Principle:

Polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision testing was done in accordance with CLSI/NCCLS Approved Guideline for Evaluation of Precision Performance of Clinical Devices: EP5-A2. Specimens at each level were analyzed in duplicate, twice a day, for 20 days. The repeatability and within-lab standard deviations (SD) and percent coefficient of variation (%CV) were calculated by the analysis of variance method. The data are summarized below.

hsCRP Precision Data Summary

Material	Mean mg/L	Repeatability SD (%CV)	Within-Lab SD (%CV)
hsCRP CON L	1.15	0.06 (4.8)	0.06 (5.4)
hsCRP CON H	3.46	0.14 (4.0)	0.15 (4.4)
Serum pool	2.39	0.13 (5.2)	0.13 (5.2)
Serum pool	6.50	0.33 (5.0)	0.37 (5.7)
Serum pool	7.72	0.36 (4.6)	0.42 (5.4)

b. *Linearity/assay reportable range:*

The reportable range of 0.16 – 9.5 mg/L is based on linearity, detection limit and method comparison.

Linearity across the assay range was confirmed by testing serum samples with high concentrations of CRP. These samples were serially diluted with System Diluent down to the lower measuring range (7.90 to 0.22 mg/L) in 13 points. Each dilution was tested in replicates of five. Percent recovery was calculated using the formula: Mean of test/ expected concentration X 100.

The linear regression was calculated.

Slope	Intercept	Correlation Coefficient
1.012	0.097	0.998

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

Standard values are assigned to a master calibrator lot using CRM 470.

Values are then assigned to the commercial calibrator (human pooled at target concentration) versus master calibrator using three reference curves, 4 runs, 3 vials, 4 replicates per vial tested on two nephelometric instruments for a total of 144 measurements.

Control values are assigned to a master control lot using CRM 470. Values are then assigned to the commercial control (human pooled at target concentration) versus master control using three reference curves, 4 runs, 3 vials, 4 replicates per vial tested on two nephelometric instruments for a total of 144 measurements.

Standard stability is tested real time for stored at +2 to +8°C and opened/punctured on board instrument.

d. *Detection limit:*

The claimed limit of quantification is 0.16

The limit of quantification claim is based on a single lot dependent calibrator, which is serially diluted into seven levels. The limit of quantification was empirically calculated based on historical variability of the calibrator. This was confirmed with analytical sensitivity and functional sensitivity testing.

Confirmed functional sensitivity with a % CV is 0.08 mg/L

Analytical Sensitivity is 0.011mg/L based on the mean value of twenty replicates of System Diluent plus two standard deviations

e. *Analytical specificity:*

HIL Interference

The CardioPhase® hsCRP method was evaluated for interference according to CLSI/NCCLS EP7-A2. Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Bias exceeding 10% is considered interference.

Substance Tested	Substance Concentration	S. I. Units	CRP Concentration mg/L	Bias %
Hemoglobin (hemolysate)	1000 mg/dL	0.62 mmol/L	0.93	+1
Bilirubin (unconjugated)	60 mg/dL	1026 µmol/L	0.97	-3
Bilirubin (conjugated)	60 mg/dL	1026 µmol/L	0.97	+1
Lipemia (Triglycerides)	1455 mg/dL	16.4 mmol/L	2.48	+4

Non Interfering Substances

The following substances do not interfere with the CardioPhase® hsCRP method when present in serum and plasma at the concentrations indicated. Inaccuracies (biases) due to these substances are less than 10% at CRP concentration of 0.23 mg/L to 8.07 mg/L.

Substance	Test Concentration	S. I. Units
Acetaminophen	0.025 mg/dL	1.66 µmol/L
Amikacin	15 mg/dL	256 µmol/L
Ammonium heparin	3 U/mL	3000 U/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic acid	5 mg/dL	227 µmol/L
Caffeine	6 mg/dL	308 µmol/L
Carbamazepine	3 mg/dL	127 µmol/L
Chloramphenicol	5 mg/dL	155 µmol/L
Chlordiazepoxide	1 mg/dL	33.3 µmol/L
Chlorpromazine	0.2 mg/dL	6.27 µmol/L
Cholesterol	500 mg/dL	12.9 mmol/L

Substance	Test Concentration	S. I. Units
Cimetidine	2 mg/dL	79.2 µmol/L
Creatinine	30 mg/dL	2652 µmol/L
Dextran 40	6000 mg/dL	1500 µmol/L
Diazepam	0.5 mg/dL	17.6 µmol/L
Digoxin	5 ng/dL	6.15 nmol/L
Erythromycin	6 mg/dL	81.6 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25 mg/dL	1770 µmol/L
Furosemide	6 mg/dL	181 µmol/L
Gentamicin	12 mg/dL	251 µmol/L
Ibuprofen	50 mg/dL	2425 µmol/L
Immunoglobulin G (IgG)	5 g/dL	50 g/L
Lidocaine	1.2 mg/dL	51.2 µmol/L
Lithium chloride	2.3 mg/dL	3.2 mmol/L
Lithium heparin	3 U/mL	3000 U/L
Nicotine	0.1 mg/dL	6.2 µmol/L
Penicillin G	25 U/mL	25000 U/L
Pentobarbital	8 mg/dL	354 µmol/L
Phenobarbital	10 mg/dL	431 µmol/L
Phenytoin	5 mg/dL	198 µmol/L
Primidone	4 mg/dL	183 µmol/L
Propoxyphene	0.2 mg/dL	4.91 µmol/L
Protein Albumin	6 g/dL	60 g/L
Protein Total	10 g/dL	100 g/L
Rheumatoid Factor	500 IU/mL	500 IU/mL
Salicylic acid	60 mg/dL	4.34 mmol/L
Sodium heparin	3 U/mL	3000 U/L
Theophylline	4 mg/dL	222 µmol/L
Urea	500 mg/dL	83.3 mmol/L
Uric Acid	20 mg/dL	1190 µmol/L
Valproic acid	50 mg/dL	3467 µmol/L

The CardioPhase® hsCRP method shows no hook effect up to 1302.2 mg/L.

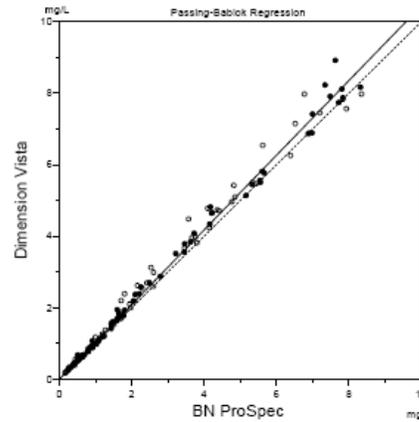
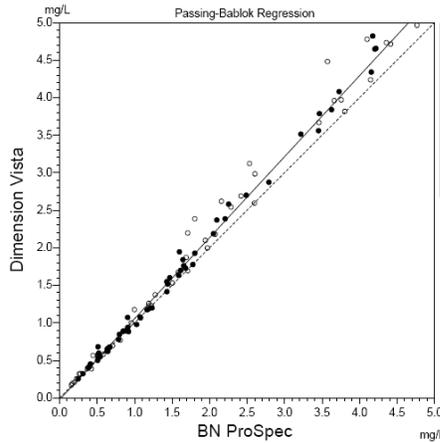
f. *Assay cut-off:*
Not Applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

The Dimension Vista™ CardioPhase® hsCRP assay was compared to the Dade Behring CardioPhase® hsCRP assay on the BN ProSpec® System by evaluating serum and plasma samples with concentrations ranging from 0.169 to 8.922 mg/L. Regression analyses of these results yielded the following equations:

Dimension Vista™ hsCRP	N	Slope	Intercept	Correlation Coefficient
0.16 to 9.5 mg/L	133	1.044	+0.003	0.995
0.16 to 5.0 mg/L	104	1.079	-0.026	0.995



b. Matrix comparison:

Sample	Serum	Li Hep	Na Hep
1	0.25	0.24	0.24
2	0.85	0.82	0.85
3	1.05	1.07	1.07
4	1.21	1.16	1.15
5	1.31	1.32	1.39
6	3.92	3.82	3.91
7	5.31	5.60	5.10
8	5.33	5.62	5.74
9	7.33	7.43	7.42
10	8.60	8.59	8.76

Linear Regression vs Serum

Slope:	1.02	1.02
Y-int:	-0.01	-0.02
r:	0.999	0.999
Syx:	0.13	0.16
Slope		
95% CI		
Low:	0.98	0.98
Slope		
95% CI		
High:	1.05	1.06

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):
Analytical bridging was provided to the predicate device (k033908) which had substantial peer-reviewed literature to support clinical cardiac claims. A recent AHA/CDC expert panel recommendation statement using evidence-based processes concluded that cardiac claims were appropriate.
4. Clinical cut-off:
Not Applicable
5. Expected values/Reference range:
The relative risk/average hsCRP according to published literature (Circulation 2003; 107:499-511) is:
Low <1 mg/L
Average 1.0-3.0 mg/L
High >3.0 mg/L

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.