

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

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

k063057

**B. Purpose for Submission:**

New indication for use for already cleared product k003372

**C. Measurand:**

High Sensitivity C-Reactive Protein

**D. Type of Test:**

Quantitative chemiluminescent immunometric assay

**E. Applicant:**

Diagnostic Products Corporation

**F. Proprietary and Established Names:**

Immulite/Immulite 1000, Immulite 2000 High Sensitivity CRP

**G. Regulatory Information:**

1. Regulation section:

21CFR Sec.- 866.5270-C-reactive protein immunological test system.

2. Classification:

Class 2

3. Product code:

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

4. Panel:

Chemistry (75)

**H. Intended Use:**

1. Intended use(s):

See Indication(s) for use below.

2. Indication(s) for use:

The IMMULITE®/IMMULITE® 1000 High Sensitivity CRP assay is intended for use as follows:

For *in vitro* diagnostic use with the IMMULITE/IMMULITE 1000 Analyzer — for the quantitative measurement of C-Reactive protein (CRP) in serum or plasma

as an aid in the detection and evaluation of infection, tissue injury and 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 syndrome may be useful as an independent marker for recurrent events in patients with stable coronary disease or acute coronary syndrome.

IMMULITE® 2000 High Sensitivity CRP assay is intended for use as follows:

For *in vitro* diagnostic use with the IMMULITE 2000 Analyzer — for the quantitative measurement of C-Reactive protein (CRP) in serum or plasma as an aid in the detection and evaluation of infection, tissue injury and 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 syndrome may be useful as an independent marker 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:  
DPC IMMULITE®/IMMULITE® 1000 and IMMULITE® 2000 analyzers

## **I. Device Description:**

### **Materials Supplied**

Components are a matched set. Labels on the inside box are needed for the assay.

The following are included:

- CRP Bead Pack (L2CR12) with barcode. 200 beads, coated with anti-ligand. Stable at 2–8°C until expiration date. L2KCRP2: 1 pack. L2KCRP6: 3 packs.
- CRP Reagent Wedge (L2CRPA2) with barcode. 11.5 mL ligand-labeled anti-CRP murine monoclonal antibody and alkaline phosphatase (bovine calf intestine) conjugated to rabbit polyclonal anti-CRP antibody in buffer. Stable at 2–8°C until expiration date.
- L2KCRP2: 1 wedge.
- L2KCRP6: 3 wedges.
- CRP Adjustors (LCRL, LCRH) Two vials (Low and High), 2.0 mL each, of CRP in a protein/buffer matrix, with preservative. Stable at 2–8°C for 30 days after opening, or for 6 months (aliquotted) at –20°C.
- L2KCRP2: 1 set. L2KCRP6: 2 sets
- CRP Sample Diluent (L2CRZ) For the on-board dilution of patient samples. 50 mL of a concentrated (ready-to-use) CRP-free protein/buffer matrix. Stable at 2–8°C for 30 days after opening, or for 6 months (aliquotted) at –20°C.
- L2KCRP2: 1 vial. L2KCRP6: 3 vials. Barcode labels are provided for use

with the diluent.

- L2KCRP2: 3 labels. L2KCRP6: 5 labels.

**Kit Components**

Supplied Separately

L2SUBM: Chemiluminescent Substrate

L2PWSM: Probe Wash

L2KPM: Probe Cleaning Kit

LRXT: Reaction Tubes (disposable)

L2ZT: 250 Sample Diluent Test Tubes (16 × 100 mm)

L2ZC: 250 Sample Diluent Tube Caps

LCRCM: Tri-level CRP Control Module

Also Required

Distilled or deionized water; test tubes; controls.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):  
Dade Behring N High Sensitivity CRP
2. Predicate 510(k) number(s):  
K033908
3. Comparison with predicate:

Item	IMMULITE/IMMULITE 1000 and IMMULITE 2000 High Sensitivity CRP	Dade Behring N <i>High Sensitivity</i> CRP using BN™ Systems
Assay Type	Chemiluminescent immunometric	Particle enhanced immunonephelometry
Antibody	Anti-CRP Murine monoclonal and rabbit polyclonal anti-CRP	Mouse monoclonal Anti-CRP
Expected Values	<p>Expected high sensitivity CRP values for healthy individuals has been established in the literature as &lt;3 mg/L.</p> <p>A study performed on 100 apparently healthy volunteers yielded a median of 1.4 mg/L and an upper 97.5<sup>th</sup> percentile of 11 mg/L.</p> <p>The AHA/CDC Scientific Statement concerning inflammation and cardiovascular markers reports that hsCRP values &lt; 1 mg/L are low risk for cardiovascular disease prediction; values between 1–3 mg/L are average risk for cardiovascular disease prediction; and values &gt; 3 mg/L are</p>	<p>Expected values for healthy individuals as noted in the literature is &lt;3 mg/L.</p> <p>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</p> <p>A subset of the Stanisless Cohort was examined in this study. The cohort subset used consisted of 1151 males and 996 females ranging in age from 5 to 71 years. All participants were of European ancestry and free of previously diagnosed serious or chronic disease (such as cancer or cardiovascular disease) and excluded</p>

Item	IMMULITE/IMMULITE 1000 and IMMULITE 2000 High Sensitivity CRP	Dade Behring N <i>High Sensitivity</i> CRP using BN™ Systems
	<p>high risk for cardiovascular disease prediction.</p> <p>Increases in CRP are non-specific and should not be interpreted without a complete clinical history.</p> <p>Consider these limits as guidelines only. Each laboratory should establish its own reference ranges.</p>	<p>individuals taking anti-inflammatory drugs or antibiotics.</p> <p>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.</p>
Reference standards	WHO IS 85/506 and CRM 470	CRM 470
Indications for Use	<p>For <i>in vitro</i> diagnostic use with the IMMULITE/IMMULITE 1000 and IMMULITE 2000 Analyzers — for the quantitative measurement of C-Reactive protein (CRP) in serum or plasma as an aid in the detection and evaluation of infection, tissue injury and 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 syndrome may be useful as an independent marker for recurrent events in patients with stable coronary disease or acute coronary syndrome.</p>	<p>N <i>High Sensitivity</i> CRP is an <i>in vitro</i> diagnostic reagent for the quantitative determination of C-reactive protein (CRP) in human serum, and heparin and EDTA plasma by means of particle enhanced immunonephelometry using the BN Systems. 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. 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 for recurrent events in patients with stable coronary disease or acute coronary syndromes.</p>
Working Range	<p>IMMULITE/IMMULITE 1000: 0.3 to 100 mg/L</p> <p>IMMULITE 2000: 0.2 to 100 mg/L</p>	0.175 to 1100 mg/L
Analytic Sensitivity	<p>IMMULITE/IMMULITE 1000: 0.1 mg/L</p> <p>IMMULITE 2000: 0.1 mg/L</p>	0.175 mg/L
Functional Sensitivity	<p>IMMULITE/IMMULITE 1000: 0.3 mg/L</p> <p>IMMULITE 2000: 0.2mg/L</p>	Not reported in the package insert

Item	IMMULITE/IMMULITE 1000 and IMMULITE 2000 High Sensitivity CRP	Dade Behring N <i>High Sensitivity</i> CRP using BN™ Systems
Sample Type	Serum and Heparinized plasma	Serum, heparinized, and EDTA plasma
Interferences	No significant interference from conjugated bilirubin (up to 200 mg/L), hemoglobin (up to 570 mg/dL for IMMULITE/IMMULITE 1000, and 512 mg/dL for IMMULITE 2000), or triglycerides (up to 3000 mg/dL).  No cross-reactivity with human serum albumin, human IgG, or transferrin	No significant interference from bilirubin (up to 230 mg/L), hemoglobin (up to 36 g/L) or triglycerides (up to 7.4 g/L).
Hook Effect	IMMULITE/IMMULITE 1000: No high dose hook effect up to 3780 mg/L IMMULITE 2000: No high dose hook effect up to 3780 mg/L	Not reported in the package insert.
Calibration Interval	Recommended 2 week adjustment interval	Reference curve valid for 4 weeks and beyond as indicated by control results

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

- 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”, issued September 22, 2005.
- Clinical Laboratory Standard Institute (CLSI). Protocols for the Determination of Limits of Detection and Limits of Quantitation; Approved Guideline. CLSI document EP17-A Vol 24 No 34. CLSI 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004.
- Clinical Laboratory Standard Institute (CLSI). Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition. CLSI document EP5-A2. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004.

**L. Test Principle:**

IMMULITE 1000/2000 High Sensitivity CRP is a solid-phase, chemiluminescent immunometric assay. The solid phase (bead) is coated with anti-ligand. The liquid phase consists of ligand-labeled anti-CRP murine monoclonal antibody and alkaline phosphatase (bovine calf intestine) conjugated to rabbit polyclonal anti-CRP antibody in buffer.

The manually prediluted patient sample (1-in-101) for the Immulite 1000 and the automatically prediluted patient sample for the Immulite 2000 and the reagent are incubated together with the coated bead for 30 minutes. During this time, the CRP in the sample forms the antibody sandwich complex with the ligand-labeled anti-CRP murine monoclonal antibody in the reagent and the anti-ligand on the bead. The

enzyme conjugate then binds to the immobilized CRP. Unbound patient sample and enzyme conjugate are then removed by a centrifugal wash. Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

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

The assay or assay performance has not changed, but new assay performance characteristics have been established for the new indications and are presented below as applicable.

1. Analytical performance:

a. *Precision/Reproducibility:*

Not Applicable subject of k003372

b. *Linearity/assay reportable range:*

Reportable Range:

0.3 to 100 mg/L for the Immulite 1000

0.2 to 100 mg/L for the Immulite 2000

See k003372 for Linearity

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

Standardization Check against CRM 470

IMMULITE 1000

This study was performed using five IMMULITE/IMMULITE 1000

instruments over a 4-day period using two kit lots of IMMULITE/IMMULITE 1000 hsCRP.

The regression statistics below show equivalent recovery of patient samples using a calibration curve generated with the CRM 470 standards and a calibration curve generated using the IMMULITE/IMMULITE 1000 hsCRP calibrators. The CRM calibrators were prepared by the serial dilution method.

N	156
Slope	0.988 (95% CI 0.978 to 0.998)
Intercept	-0.355 (95% CI -0.762 to 0.0524) mg/L
R	0.998
Mean IMMULITE/IMMULITE 1000 calibration curve	21.4 mg/L
Mean CRM 470 calibration curve	22.0 mg/L

IMMULITE 2000 and IMMULITE 2500<sup>1</sup>

This study was performed using five IMMULITE 2000 instruments, four IMMULITE 2500 instruments, two IMMULITE 2000 hsCRP kit lots and two IMMULITE 2500 kit lots over a four day period. The IMMULITE 2000 and IMMULITE 2500 hsCRP assays are the very same reagents in two different colored boxes run under the same assay and instrument methodology, therefore the data generated on both IMMULITE 2000 and IMMULITE 2500

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<sup>1</sup> The IMMULITE 2500 uses the same reagent and parameters as the IMMULITE 2000 and is not the subject of this review but is used here establish traceability to CRM 470.

were pooled.

The regression statistics below shows equivalent recovery of patient samples using a calibration curve generated using the CRM 470 standards and a calibration curve generated using the IMMULITE 2000/IMMULITE 2500 hsCRP calibrators.

N	242
Slope	0.943 (95% CI 0.935 to 0.951)
Intercept	0.160 (95% CI -0.152 to 0.471) mg/L
R	0.998
Mean IMMULITE 2000/IMMULITE 2500 calibration curve	20.4 mg/L
Mean CRM 470 calibration curve	21.5 mg/L

Stability and expected values are the subject of k003372

*d. Detection limit:*

The IMMULITE family of instruments High Sensitivity CRP assays' analytical sensitivity is 0.1 mg/L as previously reported and cleared in Pre-market Notification 510(k) K003372 for IMMULITE/IMMULITE 1000 and IMMULITE 2000.

Additional precision performance studies for determination of functional sensitivity were conducted guided by CLSI document EP5-A2. (Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition.) and CLSI document EP17-A (Protocols for the Determination of Limits of Detection and Limits of Quantitation; Approved Guideline.)

Five serum pools were prepared at hsCRP values from 0.02 mg/L (below the analytical sensitivity of 0.1 mg/L) to the expected 10% CV functional sensitivity of 0.3 mg/L.

The functional sensitivity (lowest concentration that can be measured with a total CV% of 10%) is 0.28 mg/L on the IMMULITE/IMMULITE 1000. The Package Insert claim for the IMMULITE/IMMULITE 1000 hsCRP is 0.3 mg/L.

The functional sensitivity (lowest concentration that can be measured with a total CV% of 10%) is 0.13 mg/L on the IMMULITE 2000. The Package Insert claim for the IMMULITE 2000 is 0.2 mg/L.

*e. Analytical specificity:*

Not Applicable subject of k003372

- f. *Assay cut-off:*  
Not Applicable subject of k003372

2. Comparison studies:

- a. *Method comparison with predicate device:*  
Subject of k003372

The High Sensitivity/Cardiovascular claim was further evaluated using the same data set from the previously reviewed study in the range no greater than 10 mg/L, by linear regression (N=189, range 0.1 to 10 mg/L by Dade Behring, slope = 0.9445 95%CI 0.9235 to 0.9654, intercept = 0.0240 95%CI -0.0285 to 0.0765)

Mean Dade Behring: 1.7 mg/L  
Mean IMMULITE: 1.6 mg/L

- b. *Matrix comparison:*  
Not Applicable subject of k003372

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 its original submission (k003372) and has provided updated performance information to the DADE BEHRING, N HIGH SENSITIVITY CRP (k991385/k033908). The DADE BEHRING, N HIGH SENSITIVITY CRP assay was the device used in the clinical studies supporting an indication for cardiovascular use.

4. Clinical cut-off:  
Not Applicable

5. Expected values/Reference range:  
Expected high sensitivity CRP values for healthy individuals have been established in the literature at < 3 mg/L<sup>2</sup>.

The AHA/CDC Scientific Statement<sup>3</sup> concerning inflammation and

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<sup>2</sup> Biasucci LM. CDC/AHA workshop on markers of inflammation and cardiovascular disease. Application to clinical and public health practice clinical use of inflammatory markers in patients with cardiovascular diseases. A background paper. Circulation 2004;110:e560-e567.

<sup>3</sup> Pearson TA, Mensah GA, Alexander RW, et al. AHA/CDC Scientific Statement. 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 the American Heart Association. Circ 2003;107:499-511.



cardiovascular markers reports that hsCRP

- values < 1 mg/L are low risk for cardiovascular disease prediction;
- values between 1–3 mg/L are average risk for cardiovascular disease prediction; and
- values > 3 mg/L are high risk for cardiovascular disease prediction.

**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.