

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

A. 510(k) Number:

K053603

B. Purpose for Submission:

New assay

C. Measurand:

C-Reactive Protein

D. Type of Test:

Particle enhanced turbidimetric assay.

E. Applicant:

ROCHE DIAGNOSTICS CORP.

F. Proprietary and Established Names:

C-REACTIVE PROTEIN (LATEX) HIGH SENSITIVE TEST SYSTEM FOR
COBAS INTEGRA INSTRUMENTS

G. Regulatory Information:

1. Regulation section:

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

2. Classification:

2

3. Product code:

NQD - CARDIAC C-REACTIVE PROTEIN, ANTIGEN, ANTISERUM, AND
CONTROL

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

The CRP (Latex) High Sensitive Immunoturbidimetric assay is for the in vitro quantitative determination of C-reactive protein (CRP) in human serum and plasma on Roche automated clinical chemistry analyzers. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

2. Indication(s) for use:

The CRP (Latex) High Sensitive Immunoturbidimetric assay is for the in vitro quantitative determination of C-reactive protein (CRP) in human serum and plasma on Roche automated clinical chemistry analyzers. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart

disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

3. Special conditions for use statement(s):

Prescription use

4. Special instrument requirements:

The CRP (Latex) HS assay is intended for use on Roche automated clinical chemistry analyzers.

This submission describes applications for the Integra family of analyzers; namely, the Integra 400, 400 plus, 700, and 800. The Integra family of analyzers is cleared under K951595.

I. Device Description:

The CRP (latex) HS Test System is a latex particle-enhanced immunoturbidimetric test for the quantitative measurement of C-reactive protein in human serum or plasma. Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically. The calibrator is the Calibrator for automated systems (C.f.a.s). Proteins; and the recommended control materials are CRP T Control N and Precinorm Protein. The reagents are for use on the Integra 400, 400 plus, 700 and 800 analyzers.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Roche Tina-quant® CRP (latex) HS Test System, Dade Behring N High Sensitivity CRP

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

K042485, K033908 respectively

3. Comparison with predicate:

The CRP (latex) HS Test System for COBAS Integra instruments is compared to the currently marketed Roche Tina-quant® CRP (latex) HS Test System cleared under K042485. For purposes of cardiac risk assessment, the CRP (latex) HS system is also equivalent to the Dade Behring N High Sensitivity CRP (K033908)

The Tina-quant® CRP (Latex) High Sensitive Immunoturbidimetric assay is for the in vitro quantitative determination of C-reactive protein (CRP) in human serum and plasma on Roche automated clinical chemistry analyzers. Highly sensitive measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Both test systems are intended for the in vitro quantitative determination of C-reactive protein in human serum and plasma and have the same indications for use. Both share the same test principle - they are both latex-particle enhanced immunoturbidimetric assays. The reagents are quite similar; the active ingredients and antibodies are the same. Both are ultimately traceable to the same reference material (CRM 470).

The new test system has similar imprecision, known interferences, comparable standards and calibrators, and is comparable in absolute values to the predicate device. They share expected values and instructions for result interpretation.

This test system is intended for use on the COBAS Integra family of analyzers while the predicate device was intended for use on the Roche/Hitachi family of analyzers. There are some very minor differences in reagent composition. Compared to the predicate device, this test system has some slight differences in specific performance characteristics.

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

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: <http://www.fda.gov/cdrh/oivd/guidance/1246.html>

L. Test Principle:

The Immunoturbidimetric methodology used in this assay is well-established and is the basis for the already cleared Integra CRP assay (K981897). During the reaction, anti-CRP antibodies coupled with latex microparticles react with CRP in the sample to form an antigen-antibody agglutinate, which is measured turbidimetrically.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility was determined using human samples and controls (within run n = 21, between run n = 21).

Sample	Within-run		Between-run	
	Mean	CV	Mean	CV
	mg/L (nmol/L)	%	mg/L (nmol/L)	%
Control Level 1	3.3 (31.4)	0.9	3.3 (31.4)	3.5
Control Level 2	8.0 (76.2)	0.7	8.0 (76.2)	2.2
Human pool 1	1.6 (15.2)	1.3	1.5 (14.3)	3.1
Human pool 2	11.4 (109)	0.6	11.4 (109)	2.3

b. *Linearity/assay reportable range:*

To determine linearity of the CRP (Latex) HS test system, three dilution series of different analyte concentrations were measured as samples using the CRP (Latex) Test system on the Integra 700. The three dilution series covered the low end (0-3 mg/L); midrange (0-30mg/L) and extended measuring ranges (0-

306mg/L). The attached files show the results of these measurements. The linearity data support a linear range of 0 up to 306 mg/L. Comparable results were found on the Integra 400

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The calibrators and controls including stability claims have all been previously cleared and used with CRP test systems. Their composition has not been modified for use with the CRP (Latex) HS test system.

All calibrators and controls are traceable to the reference preparation CRM 470. All value assignments were performed under standardized conditions using CRP (Latex) HS reagents.

- d. *Detection limit:*

Analytical sensitivity (lower detection limit)

0.1 mg/L (0.952 nmol/L)

The detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying three standard deviations above that of a zero sample (zero sample + 3 SD, within run precision, n = 21).

Functional sensitivity (limit of quantitation)

0.3 mg/L (2.96 nmol/L)

The functional sensitivity (limit of quantitation) is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of <10%.

- e. *Analytical specificity:*

Interference

Criterion: Recovery within $\pm 10\%$ of initial value.

Serum, plasma

Hemolysis - No interference up to 10 g/L or 621 $\mu\text{mol/L}$ hemoglobin.

Icterus - No interference up to 0.6 g/L or 1030 $\mu\text{mol/L}$ bilirubin.

Lipemia (Intralipid) - No significant interference up to a triglycerides level of 5 g/L at 2 mg/L or 19 nmol/L CRP.

High-dose hook effect - Does not occur at CRP concentrations below 40 mg/L or 380 nmol/L. Samples with concentrations >40 mg/L are flagged either >TEST RNG or "HIGH ACT".

Rheumatoid factors - No interference up to 1200 IU/mL.

Dysproteinemia - In very rare cases, monoclonal gammopathy may lead to false CRP values due to formation of turbidity or direct interaction of the monoclonal antibody in the specimen with the test system.

HAMA - Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

- f. *Assay cut-off:*

Not Applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

Method comparison

CRP values for human serum and plasma samples obtained on a COBAS INTEGRA 700 analyzer with the COBAS INTEGRA C-Reactive Protein (Latex) cassette High Sensitive Assay (CRPHS) were compared to two commercially available alternative automated systems. Sample size (n) represents all replicates.

Roche Tina-quant® CRP (latex) HS Test System:

Values ranged from 0.2 to 16.3 mg/L (1.9 to 15.5 nmol/L).

Passing/Bablok30 Linear regression

$$y = 1.0548x + 0.0414 \quad y = 0.9877x + 0.1264$$

$$\tau = 0.956 \quad r = 0.996$$

Number of samples measured: 58

Dade Behring N High Sensitivity CRP:

Values ranged from 0.1 to 9.0 mg/L (1.0 to 8.6 nmol/L).

Passing/Bablok30 Linear regression

$$y = 0.9715x + 0.0211 \quad y = 0.9941x + 0.0295$$

$$\tau = 0.935 \quad r = 0.998$$

Number of samples measured: 54

b. *Matrix comparison:*

The studies described in this submission were all performed using serum samples. To validate the use of the additional sample types Li-heparin and K2-EDTA plasma with the CRP (Latex) HS assay; parallel samples were collected in serum, Li-heparin plasma, and K2-EDTA collection tubes and analyzed on the Integra 700 analyzer using the CRP(Latex) HS test system. The serum sample was used as the reference sample and for each plasma tube type, the deviation from the reference sample was noted. For samples < 1 mg/L CRP, the deviation was expressed in absolute terms; and for samples > 1 mg/L CRP the deviation was expressed as a percentage. The plasma sample types were considered acceptable if the average deviation for samples < 1 mg/L was < 0.1 mg/L; or 10% for samples > 1mg/L. As can be seen by the attached data, these criteria were met, supporting the method sheet recommendation of Li-heparin and K2-EDTA plasma as acceptable specimen types.

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:

Consensus reference interval for adults:

<5.0 mg/L

IFCC/CRM 470

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:

<1.0 mg/L low

1.0–3.0 mg/L average

>3.0 mg/L high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

Pearson TA 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.

5-95% reference intervals of neonates and children:

Neonates (0-3 weeks): 0.1-4.1 mg/L

Children (2 months-15 years): 0.1-2.8 mg/L

Schlebusch H, Liappis N, Kalina E, Klein G. High Sensitive CRP and Creatinine: Reference Intervals from Infancy to Childhood. J Lab Med 2002;26:341-346.

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.