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

A. 510(k) Number:
k081294

B. Purpose for Submission:
New device

C. Measurand:
C-Reactive Protein (CRP)

D. Type of Test:
Quantitative, immunoturbidimetric

E. Applicant:
Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:
Advia Chemistry Cardiophase High Sensitivity C-Reactive Protein (hsCRP)

G. Regulatory Information:

1. Regulation section:
   21CFR Sec.- 866.5270-C-reactive protein immunological test system
   21CFR Sec.- 862.1150 Calibrator

2. Classification:
   Class 2

3. Product code:
   NQD - C-Reactive Protein, Antigen, Antiserum, and Control
   JIX - Calibrator, Multi-Analyte Mixture

4. Panel:
   Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See indication(s) for use below.

2. Indication(s) for use:

   The ADVIA Chemistry CardioPhase High Sensitivity C-Reactive Protein assay is for in vitro diagnostic use in the quantitative determination of the concentration of C-Reactive Protein (CRP) in human serum and plasma (lithium heparin or

potassium EDTA) on the ADVIA Chemistry systems. In acute phase response, increased levels of a number of plasma proteins, including CRP, are 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. Measurement 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.

The ADVIA Chemistry CardioPhase High Sensitivity C-Reactive Protein Calibrators are for in vitro diagnostic use in the calibration of ADVIA Chemistry systems for the CardioPhase High Sensitivity C-Reactive Protein method.

3. Special conditions for use statement(s):
   For prescription use

4. Special instrument requirements:
   Siemens ADVIA Chemistry systems

I. Device Description:

Reagent	Component	Concentration
Reagent 1	Glycine	170 mmol/L
	Sodium Chloride	100 mmol/L
	EDTA Disodium Salt Dihydrate	50 mmol/L
	Sodium Azide	0.09% w/v
Reagent 2	CRP Antibody (rabbit) − synthetic latex	Lot specific
	Sodium Azide	0.09% w/v

Calibrator
Amount 1.0 mL/vial of 6 levels
Ingredients Recombinant human CRP in a stabilized protein matrix; sodium azide 0.09%

J. Substantial Equivalence Information:

1. Predicate device name(s):
   CardioPhase High Sensitivity C-Reactive Protein (hsCRP)
   ADVIA Chemistry Wide Range C-Reactive Protein Calibrators

2. Predicate 510(k) number(s):
   k033908, k022682

3. Comparison with predicate:

	Device	Predicate Device
Item	**ADVIA® Chemistry CardioPhase™ High Sensitivity C-Reactive Protein (hsCRP)**	**Siemens Healthcare (formerly Dade Behring) CardioPhase™ High Sensitivity CRP on the BNII Systems (formerly Dade Behring)**
Intended Use	For the quantitative determination of C-Reactive Protein (CRP) on the ADVIA Chemistry Systems	For the quantitative determination of C-Reactive Protein (CRP) using the BN Systems
Indications for Use	In acute phase response, increased levels of a number of plasma proteins, including CRP, are 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. Measurement 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.	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 of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndromes.
Specimen Type	Human serum and plasma (lithium heparin, potassium EDTA)	Human serum, heparin plasma, and EDTA plasma
Assay Principle	Latex enhanced immunoturbidimetric assay	Particle enhanced immunonephelometry assay
Reagents	Ready to use reagents (R1 and R2)	Ready to use reagent
Antibody	Rabbit Polyclonal	Mouse Monoclonal
Calibration	Multipoint calibration (6 levels)	Reference curves generated by multi-point calibration
Calibrator	ADVIA Chemistry CardioPhase™ High Sensitivity C-Reactive Protein Calibrators	N Rheumatology Standard SL N Diluent
Analytical Range*	0.16 – 10.0 mg/L	0.175 to 20 mg/L
Standardization	IRMM Reference Material CRM 470	IRMM Reference Material CRM 470

	Device	Predicate
Item	**ADVIA® Chemistry CardioPhase™ High Sensitivity CRP Calibrators**	**ADVIA® Chemistry Wide Range CRP Calibrators**
Intended Use	For *in vitro* diagnostic use in the calibration of ADVIA Chemistry systems for the CardioPhase hsCRP method	For *in vitro* diagnostic use in the calibration of ADVIA Chemistry systems for the wrCRP method
Specimen Type (calibrated method)	Human serum and plasma	Human serum and plasma
Matrix	Liquid	Liquid
Instructions for Use (Preparation)	The calibrators are ready to use	The calibrators are ready to use
Calibrator Levels	6	6
Calibrator Ingredients	Recombinant human CRP in a stabilized protein matrix; contains sodium azide	Recombinant human CRP in a stabilized protein matrix; contains sodium azide
Expected Values	Lot specific: 0, 0.53, 1.05, 1.58, 5.25, and 10.50 mg/L	Lot specific: 0, 2.5, 10, 20, 80, and 160 mg/L
Standardization	CRM-470	CRM-470

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

CLSI - Evaluation of Precision Performance of Clinical Chemistry Devices - EP05-A2
CLSI - Evaluation of the Linearity of Quantitative Analytical Methods - EP06-A
CLSI - Protocols for Determination of Limits of Detection and Limits of Quantitation - EP17-A

L. Test Principle:

The CardioPhase hsCRP latex reagent is a suspension of uniform polystyrene latex particles coated with anti-CRP antibody. When serum or plasma containing CRP is mixed with the latex reagent, agglutination takes place resulting in an increase in turbidity. This turbidity is measured at 571 nm. The CRP concentration in serum or plasma is determined from a calibration curve that is generated with the calibrator materials.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. *Precision/Reproducibility:*
   Within run and total imprecision were evaluated by testing five serum pools and three levels of control materials. Each sample was assayed 2 times per run and 2 runs per day for 10 days. All runs were done with one instrument calibration. Precision estimates were computed according to CLSI document EP05-A2, Evaluation of Precision Performance of Quantitative Measurement

Methods; Approved Guideline.

		Within-run		Total	
Specimen type	*CRP Level (mg/L)*	*SD*	*CV (%)*	*SD*	*CV (%)*
BR Control 1	0.42	0.01	2.9	0.01	3.5
BR Control 2	1.83	0.01	0.7	0.02	0.9
BR Control 3	5.39	0.05	0.9	0.05	1.0
Serum Pool-low	0.16	0.01	5.3	0.01	6.8
Serum Pool	0.21	0.01	3.2	0.01	4.2
Serum Pool	1.04	0.01	1.1	0.01	1.2
Serum Pool	3.12	0.03	0.8	0.04	1.3
Serum Pool	10.27	0.14	1.4	0.16	1.6

BR Control = BioRad Liquicheck™ Cardiac Markers Plus Controls

b. Linearity/assay reportable range:

The assay range of this method is from 0.16 mg/L to 10 mg/L based on Functional Sensitivity (Limit of Quantitation, LOQ) see detection limit below, to the CRP concentration of the highest level linearity.

The linearity of this method was evaluated following the guidelines of CLSI EP6-A protocol where recombinant CRP was spiked into pooled human serum for the high CRP level, which was then diluted with a zero pool to make nine equally spaced linearity pools within the assay range. The observed CRP results on the ADVIA 1650 were compared with the expected CRP concentration. The resulting recovery information is presented in the table below:

Linearity pool	*Expected mg/L (calculated)*	*Mean Observed (n=3) mg/L*	*%Recovery (vs. Expected)*
Level 1	0.00	0.00	NA
Level 2	1.59	1.54	96.80
Level 3	3.18	3.13	98.58
Level 4	4.76	4.70	98.62
Level 5	6.35	6.23	98.11
Level 6	7.94	7.69	96.92
Level 7	9.53	9.26	97.22
Level 8	11.11	10.81	97.31
Level 9	12.70	12.70	100.00

Testing the nine samples, the resulting linear regression equation was obtained: Slope = 0.9857 (0.9651 to 1.0062), Intercept = - 0.0303 (-.1857 to 0.1252), r = 0.9997

Recovery at the lower end of the range was also shown with serial dilutions of the CRM 470 reference material. The linear regression equation obtained from testing the 4 samples was: Slope = 0.9730 (0.9020 to 1.0440), Intercept = -0.0017 (-0.1620 to 0.1587), r = 0.9997

ADVIA 1650 Low End
Linearity Data

Linearity Pool	Expected (mg/L)	Observed (mg/L)	Recovery%
level 1	0.490	0.511	104.270
level 2	0.980	0.939	95.857
level 3	1.960	1.862	95.020
level 4	3.920	3.833	97.776

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

Traceability to CRM 470 is claimed for the calibrator materials.

The ADVIA® Chemistry CardioPhaseTM High Sensitivity C-Reactive Protein (hsCRP) Calibrators are used to calibrate the hsCRP method. The calibrators consist of six (6) levels of protein stabilized matrices containing varying concentrations of recombinant human CRP (synthesized in bacteria - not human source). The Calibrators have targeted expected values (lot specific) of 0, 0.53, 1.05, 1.58, 5.25, and 10.50 mg/L, and these values are traceable to IRMM reference material CRM 470.

Shelf Life Stability

The ADVIA Chemistry hsCRP calibrator materials have a shelf stability of 18 months stored at 2 – 8°C, and have open-vial stability of 60 days when stored at 2 – 8°C.

Real Time:

The Shelf Life of the ADVIA Chemistry hsCRP calibrator materials was evaluated with Real Time Stability testing at the recommended storage temperature (2 – 8°C). Two lots of calibrators were tested at Day 0 (QC release) and at 19 months (for one lot) and at 117 weeks (or 27 months for another lot), respectively.

Open Vial:

Open Vial Stability of the ADVIA Chemistry hsCRP calibrator materials was tested up to 60 days (64 days for the 2nd lot). On Day 0, calibrators were used

to calibrate ADVIA 1650 hsCRP method, and recoveries of the controls were obtained using this calibration. The opened calibrator vials (each level) were then recapped and stored at 2 – 8°C. At each checkpoint following Day 0, these stored, opened vials of calibrators were used for calibration and control recovery, and compared to control recoveries from calibration with freshly opened vials of calibrators.

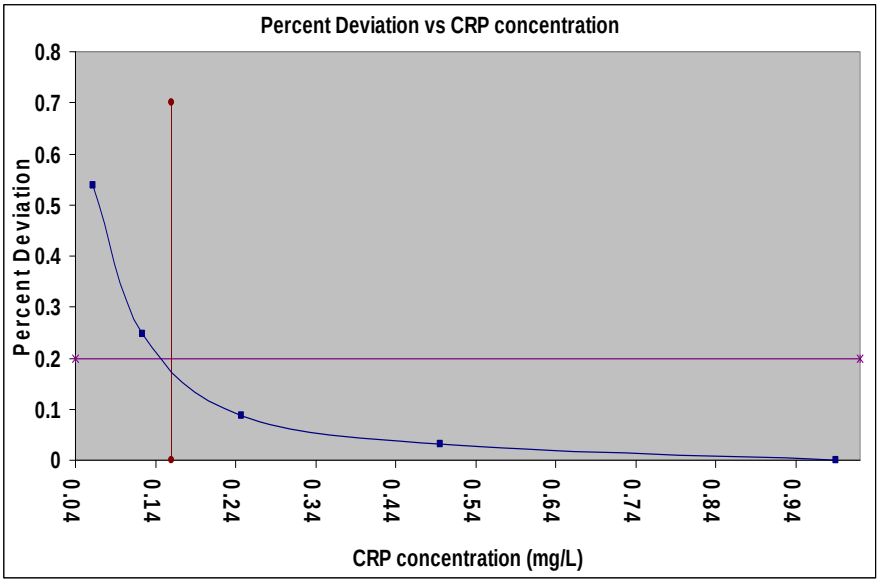
The sponsor's acceptance criteria are as follows: less than + 10% difference in control recovery using calibration with open calibrator materials versus calibration with fresh calibrator materials

d. Detection limit:

The functional sensitivity (Limit of Quantitation) of this assay is 0.16 mg/L, which is the lowest CRP concentration in a sample where total imprecision is less than 10%.

CRM 470 material was serially diluted to 0.99 mg/L, 0.495 mg/L, 0.247 mg/L, 0.124 mg/L and 0.062 mg/L. Each level was run at 8 reps/run, 5 runs total (40 reps total) on the ADVIA 1650. %CV and % deviation from the target were calculated. To determine the CRP concentration at which 20% deviation of accuracy and 10% precision and the observed recovery vs. deviation from target data was plotted.

Target	Recovered	CV%	Deviation%
0.990	0.990	1.41	0.0%
0.495	0.510	1.58	3.1%
0.247	0.269	2.35	8.8%
0.124	0.154	5.11	24.6%
0.062	0.095	6.64	53.7%



e. *Analytical specificity:*
Interference was evaluated by spiking human serum pools with hemoglobin (from lysed human red blood cells), unconjugated (free) bilirubin, conjugated bilirubin, triglycerides (Intralipid) and Rheumatoid Factor (RF). Multiple levels of each of the interfering substances were tested at a clinically relevant CRP concentration. Samples were assayed in duplicate. The results for each analyzer are presented in the labeling. There was no significant interference for bilirubin up to 30 mg/dL, for hemolysis up to 500 mg/dL, lipemia up to 750 mg/dL and rheumatoid factor up to 1040 IU/mL.

All results passed Siemens Diagnostics internal acceptance criteria for interference of ≤10% up to the acceptable level of interferent.

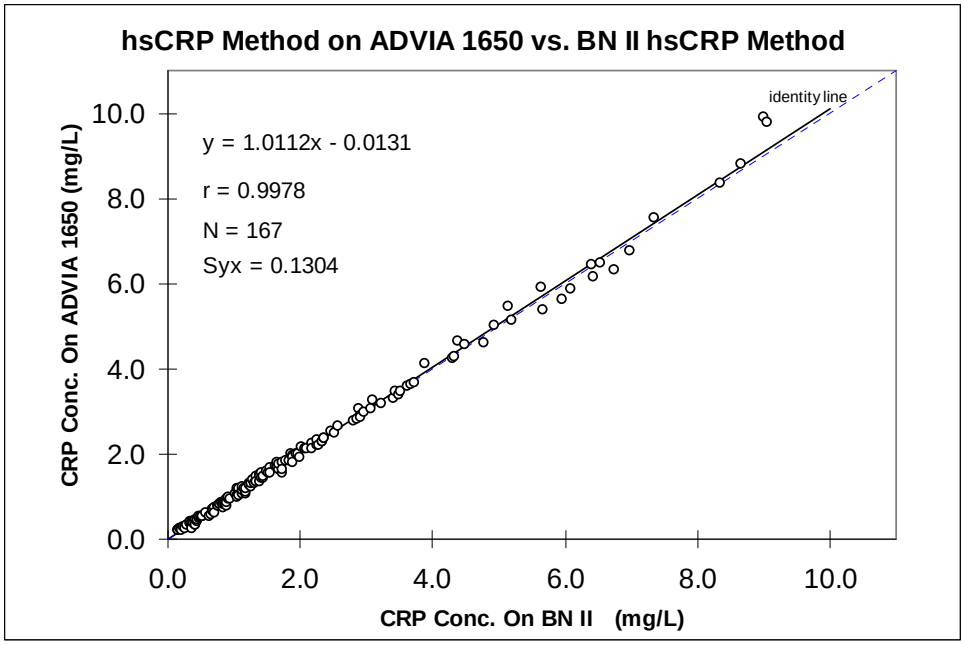
The labeling includes a limitation that there is a potential that heterophilic antibodies may interfere with this method. Also, the labeling includes a statement that the performance of this method has not been evaluated with patients containing heterophilic antibodies.

f. *Assay cut-off:*
Not Applicable

2. Comparison studies:
a. *Method comparison with predicate device:*
The ADVIA Chemistry CardioPhase hsCRP correlation studies were performed on the ADVIA 1650, against the Siemens CardioPhase High Sensitivity CRP assay on the BNII instrument.

The correlation studies were done over 7 days using 167 patient serum samples. Testing was done in duplicate on the ADVIA 1650 and in singlicate on the BNII; the data was processed using only the first result from the ADVIA 1650 (singlicate).

Comparison method	*N*	*Slope (95% CI)*	*Intercept (95% CI)*	*Sy.x*	*r*	*Sample range (mg/L)*
BNII hsCRP (Least squares)	167	1.01 (1.00 – 1.02)	-0.01 (-0.04 – 0.02)	0.1304	0.9978	0.17 – 9.05



b. Matrix comparison:
The serum/plasma equivalency study was done on the ADVIA 1650 using lithium heparin and potassium EDTA plasma samples and their corresponding serum samples. A total of 29 matched samples were tested in duplicate; some samples (6) were spiked with recombinant CRP to span the reporting range.

Matrix tested	*N*	*Slope (95% CI)*	*Intercept (95% CI)*	*Sy.x*	*r*	*Sample range* (mg/L)
Plasma (Potassium EDTA); least squares	58	0.97 (0.96 – 0.98)	0.00 (-0.06 – 0.05)	0.1451	0.9986	0.14 – 9.56
Plasma (Li Hep); least squares	58	0.98 (0.97 – 0.99)	0.00 (-0.04 – 0.04)	0.1004	0.9994	0.14 – 9.56

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):
   The method comparison studies between the device and the former Dade Behring CardioPhase™ hsCRP on the BNII system (this predicate device was used in the clinical studies supporting an indication for cardiovascular use) demonstrate acceptable correlation between both methods, thus the performance and accuracy of the device is substantially equivalent to those of the predicate device.

4. Clinical cut-off**:**
   Not Applicable

5. Expected values/Reference range:
   The expected values provided in the labeling for healthy individuals as noted in the literature are typically ≤ 3 mg/L.

   The below referenced AHA/CDC Scientific Statement concerning inflammation and cardiovascular markers also reports that CRP 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.

   Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular diseases; 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.

   Studies performed by Siemens on 190 apparently healthy volunteers yielded a median serum CRP concentration of 1.21 mg/L and an upper 97.5th percentile serum CRP concentration of 7.59 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.