

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k072658

B. Purpose for Submission:

New Device

C. Measurand:

C-Reactive Protein (CRP)

D. Type of Test:

Latex-enhanced turbidimetric immunoassay, quantitative

E. Applicant:

Seimens Medical Solutions Diagnostics

F. Proprietary and Established Names:

ADVIA™ Chemistry C-Reactive Protein_2 (CRP_2) Assay

ADVIA™ Chemistry C-Reactive Protein_2 Calibrators

G. Regulatory Information:

1. Regulation section:

866.5270 C-reactive protein immunological test system

862.1150 Calibrator

2. Classification:

Class II

3. Product code:

DCN System, test, c - reactive protein

JIX Calibrator, multi-analyte mixture

4. Panel:

Immunology

Clinical Chemistry

H. Intended Use:

1. Intended use(s):

The ADVIA™ Chemistry C-Reactive Protein_2 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) on the ADVIA Chemistry systems. Such measurements are used in the evaluation of infection, tissue injury, inflammatory disorders, and associated diseases. Increases in CRP values are non-specific for many disease processes and should not be interpreted without a complete clinical evaluation.

The ADVIA Chemistry C-Reactive Protein_2 Calibrators are for in vitro diagnostic use in the calibration of ADVIA Chemistry systems for the C-Reactive Protein_2 (CRP-2) method.

2. Indication(s) for use:

Same as above

3. Special conditions for use statement(s):

Prescription use

4. Special instrument requirements:
 ADVIA Chemistry system (1200/1650/1800/2400)

I. Device Description:

The ADVIA™ Chemistry C-Reactive Protein_2 assay consists of two liquid, ready-to-use components: Reagent 1 is a glycine buffer solution; Reagent 2 is a suspension of uniform polystyrene latex particles coated with rabbit anti-CRP antibody.

The ADVIA Chemistry C- Reactive Protein_2 Calibrators consist of six (6) levels of protein stabilized matrices containing varying concentrations of recombinant human CRO. The Calibrators have targeted expected values (lot specific) of 0, 5, 20, 40, 160 and 320 mg/L. The Calibrators (1 mL/vial) are liquid and ready to use. Storage is at 2-8°C.

J. Substantial Equivalence Information:

1. Predicate device name(s):
 ADVIA Chemistry C-Reactive Protein_2 Wide Range Calibrators
 ADVIA Chemistry C-Reactive Protein (CRP)
2. Predicate K number(s):
 k022682
 k992662
3. Comparison with predicate:

ADVIA Chemistry C-reactive Protein_2

Similarities		
Item	New Device	Predicate
Intended Use	For in vitro diagnostic use in the quantitative determination of C-reactive Protein. measurements are used in the evaluation of infection, tissue injury, inflammatory disorders, and associated diseases. Increases in CRP values are non-specific for many disease processes and should not be interpreted without a complete clinical evaluation.	Same
Expected Values	< 10 mg/L	Same
Reagent matrix	Two liquid, ready-to use	Same
Capture Antibody	Rabbit anti-CRP	Same
Storage	2-8°C	Same
Standardization	CRM-470	Same
Calibration	6-point	Same

Differences		
Item	Device	Predicate
Specimen Type	Serum or plasma (lithium heparin)	Serum
Assay Principle	Latex turbidimetric immunoassay	Polyethylene glycol assisted turbidimetric immunoassay
Read wavelength	571 nm	340/694 nm
Analytical range	4 to 336 mg/L	5-205 mg/L
On-board stability	60 days	30 days

ADVIA Chemistry C-Reactive Protein_2 Calibrators

Similarities		
Item	Device	Predicate
Intended Use	For in vitro diagnostic use in the calibration of ADVIA Chemistry systems for the CRP_2 method.	For in vitro diagnostic use in the calibration of ADVIA Chemistry systems for the wrCRP method.
Measurand	Recombinant human CRP	Same
Levels	6 point calibration; 1 mL each	Same
Matrix	Liquid, Ready-to-use	Same
Traceability	CRM470	Same
Shelf life	18 months at 2-8°C	Same

Differences		
Item	Device	Predicate
Expected Values	0, 5, 20, 40, 160, and 320 mg/L; lot specific	0, 2.5, 10, 20, 80, and 160 mg/L; lot specific
Open-vial stability	60 days at 2-8°C	28 days at 2-8°C

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

CLSI document EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline. CLSI EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline.

L. Test Principle:

Sample is diluted by the instrument and then 40 µL of diluted sample is incubated with a buffer (Reagent 1). Reagent 2, a CRP_2 latex reagent, which is a suspension of uniform polystyrene latex particles coated with rabbit anti-CRP antibody, is added 10 minutes later. When serum or plasma containing CRP is mixed with the latex

reagent, agglutination takes place resulting in an increase in the 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 CRP_2 calibrators.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Within-run and total precision were evaluated by testing three serum pools and 3 control levels on the ADVIA 1650. Samples were evaluated in duplicate in 2 runs per day for 10 days. Precision was evaluated using calculation methods in CLSI EP-5A2. Acceptance criteria (described below) were met.

Sample	Level mg/L	Within-run		Total	
		SD	CV(%)	SD	CV(%)
Control 1	31	0.33	1.1	0.38	1.3
Control 2	56	0.51	0.9	0.61	1.1
Control 3	83	1.11	1.3	1.27	1.5
Serum Pool 1*	12.8	0.50	3.9	0.50	3.9
Serum Pool 2	221	2.48	1.1	3.24	1.5
Serum Pool 3*	310.7	22.86	7.4	22.86	7.4

*5-day protocol

The acceptance criteria for precision performance are as follows:

C-RP concentration	Acceptance Criteria	
	Within-run CV	Total CV
Lower range (~10 mg/L)	5%	8%
Upper range	≤ 10%	12%

Additionally, CRP_2 Control recoveries on each platform must be within ± 5% of the ADVIA 1650.

b. *Linearity/assay reportable range:*

Linearity was evaluated by making equally spaced dilutions of a high serum pool with a low serum pool and comparing the expected vs. observed CRP concentration. Difference in recovery was ≤ 3.5%. Linear regression statistics demonstrated that the slope (and 95% CI) was 1.01 (0.987 to 1.034), y-intercept -0.10 (-4.35 to 4.14); r= 1.0.

ADVIA 1650 CRP_2 (mg/L)			
Sample	Expected	Observed	Recovery (%)
P1	0		NA
P2	38	38	100.6%
P3	76	75	98.7%
P4	114	115	100.5%

ADVIA 1650 CRP_2 (mg/L)			
Sample	Expected	Observed	Recovery (%)
P5	152	156	102.3%
P6	190	189	99.4%
P7	228	236	103.5%
P8	267	270	101.1%
P9	305	305	100.0%

The ADVIA Chemistry system has an ‘auto-dilution’ option to extend the measuring range above CRP concentrations of 304 mg/L (highest level calibrator). Samples above this are automatically diluted 3-fold by the system. The extended linearity of the ADVIA 1650 assay was evaluated by making equally spaced dilutions of two serum pools and comparing expected vs. observed CRP concentrations. Difference in recovery was $\leq 8.3\%$. Linear regression statistics for the entire assay range (0 to 1071 mg/L) demonstrated that the slope (and 95% CI) was 1.033 (1.001 to 1.064), intercept was 2.04 (-12.85 to 16.94), $r=0.999$.

ADVIA 1650 CRP_2 (mg/L)			
Sample	Expected	Observed	Recovery (%)
P1	337	337	100.0%
P2	521	542	104.1%
P3	704	763	108.3%
P4	888	942	106.2%
P5	1071	1071	100.0%

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Traceable to CRM-470.

Data and testing methodology were provided to support the open and closed stability claims in the labeling. Closed stability: 18 months at 2-8°C; On-board stability 60 days. Calibrator stability 60 days 2-8°C.

- d. *Detection limit:*

The Limit of detection (LoD) was obtained using the mean and SD of a blank and a low sample containing CRP (~3mg/L); and computed according to CLSI EP-17A protocol and determined to be 0.2 mg/L, n=40. The data support the low end claim for the analytical range as 4 mg/L.

- e. *Analytical specificity:*

Interference was evaluated by spiking human serum pools with hemoglobin (max 1000 mg/dL), unconjugated and conjugated bilirubin (max 60mg/dL), Intralipid and avian triglycerides (max 1000 mg/dL), and rheumatoid factor (200 IU/mL). Multiple levels up to the maximum concentration listed of each of the interfering substances were tested at CRP concentration of ~5 mg/L. Interference was also tested on samples containing 10 mg/L CRP using a single concentration of interferent (highest evaluated). All results passed the acceptance criteria for interference of $\leq 10\%$.

Prozone: No hook effect demonstrated up to 1000mg/L of CRP.

Cross-reactivity: cross-reactivity to other substances was not evaluated.

f. *Assay cut-off:*
Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

The CRP_2 method on the ADVIA 1650 was compared to the ADVIA Chemistry CRP method on the same analyzer using the 35 samples that spanned the assay range. The mean of duplicate measurements were analyzed by Passing-Bablok regression analysis yielding the following results:

Comparison Method (x)	N	Slope (95% C.I.)	Intercept (95% C.I.)	R	Sample Range
ADVIA Chemistry CRP	35	0.970 (0.938 to 1.00)	0.71 (-1.48 to 2.56)	0.99	6.5 to 192.3 mg/L

b. *Matrix comparison:*

A matrix comparison study was performed using matched serum and lithium-heparin plasma samples spanning the range of the assay. The results demonstrated equivalence between the matrices. Least square regression demonstrated the results:

N	Slope (95% C.I.)	Intercept (95% C.I.)	R	Sample Range
56	0.999 (0.987 – 1.011)	-0.01 (-1.61 – 1.60)	0.999	6- 246 mg/L

3. Clinical studies:

a. *Clinical Sensitivity:*
Not available.

b. *Clinical specificity:*
Not available.

c. Other clinical supportive data (when a. and b. are not applicable):
Not applicable

4. Clinical cut-off:

Not available.

5. Expected values/Reference range:

<10 mg/L (according to Tietz Clinical Guide to Laboratory Tests, 4th edition)

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.