

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

A. 510(k) Number:

k113809

B. Purpose for Submission:

New device

C. Analyte:

C-reactive protein (CRP) in human serum and plasma

D. Type of Test:

Automated latex agglutination turbidimetric immunoassay for the quantitative measurement of CRP

E. Applicant:

Hitachi Chemical Diagnostics, Inc

F. Proprietary and Established Names:

Hitachi Clinical Analyzer S TEST reagent cartridge C-Reactive Protein (CRP)

G. Regulatory Information:

1. Regulation section:

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

2. Classification:

Class II

3. Product code:

DCN – System, Test, C-reactive protein

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

The Hitachi Clinical Analyzer S TEST reagent cartridge CRP is intended for the quantitative measurement of C-reactive protein in serum, lithium heparin plasma, K3-EDTA plasma, and sodium citrate plasma. The test system is intended for use in clinical laboratories or physician office laboratories. CRP measurements aid in the evaluation of injury to body tissues, and infection and inflammatory disorders. For *in vitro* diagnostic use only.

2. Indication(s) for use:

Same as Intended use

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

For use on the Hitachi Clinical analyzer (previously cleared under k111753).

I. Device Description:

The S TEST reagent cartridges for CRP are made of plastic and include two small reservoirs capable of holding two separate reagents, separated by a reaction cell/photometric cuvette. The cartridges also include a dot code label that contains all chemistry parameters, calibration factors, and other production-related information (e.g., expiration dating).

J. Substantial Equivalence Information:

1. Predicate device name and Predicate K number

Roche C-Reactive Protein Latex (CRPLX), k073277

Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative determination of CRP	Same
Specimen type	Serum and Plasma (lithium heparin, K3-EDTA, sodium citrate)	Same
Testing Environment	Physician office or clinical lab	Same
Detection Limit	1 mg/L	Same

Differences		
Item	Device	Predicate
Test Principle	Latex agglutination turbidimetry	Particle-enhanced immunoturbidimetry
Reportable Range	1 to 150 mg/L	1 to 250 mg/L
Detection Wavelength	570/800 nm	546 nm
Linearity	1 to 154 mg/L	1 to 250 mg/L
Precision	%CVs range from 7.7% (mean 15.6 mg/L) to 2.8% (mean 122.1 mg/L)	%CVs range from 0.9% to 2.5% (from product labeling)
Instrument	Hitachi Clinical Analyzer	Roche cobas 8000

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP7-A2: Interference Testing in Clinical Chemistry, Approved Guideline – Second Edition

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

CRP in specimen reacts with goat anti-human C-reactive protein antibody that is coated on latex to induce agglutination. The concentration of CRP can be determined by measuring this agglutination as the amount of change in absorbance.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

- a. *Precision/ Reproducibility:* The studies followed CLSI EP5-A2, where three (3) levels of serum samples were each tested in-house in two runs, twice a day, for twenty (20) days. Results met the Acceptance criteria for % CV ($\leq 10\%$ for CRP up to 50 mg/L and $\leq 5\%$ for CRP at or above 50 mg/L).

Within-run precision

Samples	Mean CRP (mg/L)	SD (mg/L)	%CV
Low CRP	6.0	0.34	5.7
Middle CRP	15.6	1.16	7.4
High CRP	122.1	3.01	2.5

Total precision

Samples	Mean CRP (mg/L)	SD (mg/L)	%CV
Low CRP	6.0	0.44	7.3
Middle CRP	15.6	1.20	7.7

High CRP	122.1	3.41	2.8
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Precision studies were also performed at three external physician's office laboratory (POL) sites where three (3) blinded serum samples with low, middle, and high concentrations of CRP were assayed six times per day for five days with 3 lots of reagents. Results met the Acceptance criteria (maximum %CV of 10% for levels of 10 mg/L or greater, and a maximum SD of 1 for levels less than 10 mg/L).

Site	Sample	Mean CRP(mg/L)	Within-Run Precision		Total Precision	
			SD	%CV	SD	%CV
Site 1	Low	3.9	0.2	5.9%	0.3	6.6%
Site 2	Low	3.6	0.4	12.4%	0.5	14.1%
Site 3	Low	3.9	0.4	11.6%	0.4	11.2%
Site 1	Middle	49.7	1.9	3.8%	1.7	3.5%
Site 2	Middle	52.3	1.5	2.8%	1.5	2.9%
Site 3	Middle	54.1	1.2	2.3%	2.1	3.9%
Site 1	High	95.5	5.1	5.3%	5.3	5.6%
Site 2	High	92.3	4.0	4.3%	6.5	7.1%
Site 3	High	94.0	3.5	3.7%	4.0	4.2%

b. Linearity/assay reportable range:

Eleven serial dilutions were prepared using a commercial CRP calibration sample set. They were tested in duplicate by the Hitachi Clinical analyzer. The percent recovery was determined by comparing the measured value of CRP to the assigned reference value. Results met the Acceptance criteria for % recovery ($\pm 10\%$). The CRP assay is linear between 1 mg/L and 154 mg/L and the claimed measuring range is 1 mg/L to 150 mg/L.

Sample	Assigned	Rep 1	Rep 2	Mean	% Recovery
1	0	0	0	0	N/A

Sample	Assigned	Rep 1	Rep 2	Mean	% Recovery
2	1	1	1	1	100%
3	2	2	2	2	100%
4	4	4	4	4	100%
5	18	19	18	18.5	103%
6	27	30	28	29	107%
7	36	36	37	36.5	101%
8	72	69	69	69	96%
9	108	107	109	108	100%
10	145	145	144	144.5	100%
11	152	151	151	151	99%
12	166	153	155	154	93%
13	181	157	159	158	88%

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

Traceability: The calibration material is traceable to IRMM Standard Reference Material ERM-DA472.

Calibrators: The S TEST Reagent Cartridge CRP assay utilizes a predefined lot-specific calibration curve that is stored in the reagent cartridge barcode.

Cartridge Shelf-life/ Stability: The S TEST reagent cartridge can be stored, unopened, at 2-8°C for 1 year based on real-time stability testing.

d. Detection limit:

The limit of blank (LoB) was determined by assaying a blank sample twenty (20) times per day for three days. The LoB value was estimated to be 0.5 mg/L. The limit of detection (LoD) was determined by assaying five (5) samples with low CRP level four times per day for three days. The LoD value was calculated as the LoB + 1.645 x SD of the low sample and was found to be 0.7 mg/L.

e. Analytical specificity:

Interference studies were performed according to EP7-A2 using two serum pools with CRP concentrations of 12 mg/L and 80 mg/L. Each sample was spiked with six

different levels of interfering substances and tested in replicates of three. For non-interference to be claimed, the mean results from the spiked samples must be within 10% or 2 mg/L (whichever is greater) of the mean of the neat samples. The data demonstrated that the CRP test system was not affected by high levels of the following substances: hemoglobin (up to 1,000 mg/dL), unconjugated bilirubin (up to 50 mg/dL), triglycerides (up to 2,000 mg/dL), and ascorbic acid (up to 50 mg/dL).

Carryover

The potential effect from carryover due to high concentration samples was assessed in duplicates as follows: a high sample targeted at 120 mg/L and a low sample targeted at 10 mg/L were assayed in alternate order with three lots of S TEST CRP cartridges and three analyzers. The data are shown below. The data demonstrate no carryover effect, as the low sample reported the correct low result (approximately 10 mg/L) with multiple lots and multiple analyzers.

Analyzer		E40-005			E40-008			E40-012		
Sample	Lot#	K1F 673	K1M 998	K2A 090	K1F 673	K1M 998	K2A 090	K1F 673	K1M 998	K2A 090
1	High	120	126	125	122	124	123	117	119	118
2	Low	11	12	12	10	11	11	11	11	12
3	High	116	122	122	112	117	117	111	115	120
4	Low	11	11	11	10	11	11	11	10	11

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

A total of 88 clinical specimens, spanning the dynamic range, were assayed in singleton and in a blinded fashion by both the S TEST reagent cartridge C-Reactive Protein on the Hitachi Clinical Analyzer and the Roche C-Reactive Protein Latex test on the Roche cobas 8000 system. Linear regression statistics are based on the balance of the paired results, and the data are as follows:

n	r	Slope (95% CI)	Intercept (95% CI)
88	0.994	0.99 (0.96 to 1.01)	0.14 (-0.64 to 0.92)

Additional method comparison study (POL accuracy) were performed at three external sites using approximately 55 blinded serum samples with CRP values ranging from 1 mg/L to 130 mg/L at each site. Linear regression analysis (least

squares) yielded the following results:

Site #	N	Range	Regression Equation	r	Slope (95% CI)	Intercept (95% CI)
1	56	1 to 122	$y = 1.02x + 0.1$	0.998	1.00 to 1.04	-0.5 to 0.6
2	56	1 to 130	$y = 1.06x - 0.2$	0.999	1.05 to 1.08	-0.4 to 0.2
3	55	1 to 125	$y = 1.03x + 0.2$	0.998	1.01 to 1.05	-0.6 to 0.8

b. Matrix comparison:

A study was performed to compare the CRP concentrations in forty-five (45) matched samples drawn from the same patients. These matched serum/plasma (sodium citrate, lithium heparin, and K3-EDTA) samples that spanned the dynamic range were assayed in singleton on the Hitachi Clinical Analyzer using S TEST reagent cartridge for CRP and the results from different plasma preparations were compared with serum results using least squares linear regression. The performance characteristics were as follows.

Serum vs Plasma	Slope (95% CIs)	Intercept (95% CI)	r
Lithium Heparin Plasma	1.00 (0.98 to 1.01)	-0.12 (-0.75 to 0.52)	0.999
K3-EDTA Plasma	0.99 (0.97 to 1.00)	0.06 (-0.55 to 0.67)	0.999
Na Citrate Plasma	1.00 (0.99 to 1.01)	-0.26 (-0.82 to 0.30)	0.999

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical Specificity:

Not applicable.

c. Other clinical supportive data (when a. is not applicable):

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Consensus reference interval for adults: < 10 mg/L (Tietz Fundamentals of Clinical Chemistry, 4th Edition, 1996).

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.