

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

A. 510(k) Number:

k083412

B. Purpose for Submission:

New 510(k)

C. Measurand:

C-Reactive Protein

D. Type of Test:

Quantitative chemiluminescent immunoassay

E. Applicant:

Mitsubishi Kagaku Iatron

F. Proprietary and Established Names:

PATHFAST hsCRP

PATHFAST® hsCRP Calibrator

G. Regulatory Information:

1. Regulation section:

21CFR 866.5270-C-reactive protein immunological test system

21 CFR 862.1150- Calibrator

2. Classification:

Class II

3. Product code:

DCN - System, Test, C-Reactive Protein

JIT – Calibrator, Secondary

4. Panel:

82 Immunology

75 Clinical Chemistry

H. Intended Use:

1. Intended use(s):

See indication(s) for use below.

2. Indication(s) for use:

PATHFAST® hsCRP test, for use with PATHFAST® analyzer, is an in vitro diagnostic test for the quantitative measurement of C-reactive protein (CRP) in heparinized or EDTA whole blood, plasma, and serum, as an aid in the detection and evaluation of the infection, tissue injury, inflammatory disorders, and associated disorders. This method is for use in clinical laboratory or point of care (POC) settings.

PATHFAST® hsCRP Calibrator is an in vitro diagnostic product for the calibration of the C-reactive protein (CRP) method on the PATHFAST® System.

3. Special conditions for use statement(s):
Prescription use
4. Special instrument requirements:
PATHFAST Analyzer

I. Device Description:

The reagent cartridge consists of 6 cartridges x 10 trays. Each reagent cartridge consists of 16 wells. All wells with exclusion of sample well (#1) and counting well (#10) are covered with an aluminum seal having a bar code. All reagents for the test are filled in each well of the reagent cartridge.

Wells	form	Ingredient	Quantity	Source
# 1	Empty	sample well		
# 2	liquid	Alkaline phosphatase conjugated anti CRP MoAb	50µL	Micro-organism Mouse
		MES Buffer		
		Na azide	<0.1%	
# 7	liquid	anti CRP MoAb coated magnetic particles	50µL	Mouse
		MOPS Buffer		
#13	liquid	Chemiluminescent substrate	100µL	
		CDP-Star		
# 11	liquid	Sample Dilution Buffer	25µL	
		MOPS Buffer		
		Na azide	<0.1%	
# 3,4,5	liquid	Washing Buffer	400µL	
		MES Buffer		
		Na azide	< 0.1%	

Calibrator materials are included in the kit and are also sold separately

1. Calibrator 1 (CAL-1) 2.0 mL x 1 bottle (liquid)
2. Calibrator 2 (CAL-2) 2.0 mL x 1 bottle (liquid)

Calibrator 2 contains human serum. Blood samples from the tissue donors was tested and found negative for Anti-HIV-1/2, HBsAg and Anti-HCV using FDA approved tests.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Diagnostic Products Corporation IMMULITE hsCRP
2. Predicate 510(k) number(s):
k003372

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Indications for use	used as an aid in the detection and evaluation of the infection, tissue injury, inflammatory disorders, and associated diseases.	used as an aid in the detection and evaluation of the infection, tissue injury, inflammatory disorders, and associated diseases.
Technology	chemiluminescent	chemiluminescent
Methodology	the analyte in the patient sample forms a sandwich with immobilized antibodies in solid state and with a detector antibody labeled with alkaline phosphatase. The reaction detected by the analyzers to calculate the sample concentration is catalyzed by the alkaline phosphatase. Both analyzers employ a photon counter to read the results, which are then converted to mg/L results	the analyte in the patient sample forms a sandwich with immobilized antibodies in solid state and with a detector antibody labeled with alkaline phosphatase. The reaction detected by the analyzers to calculate the sample concentration is catalyzed by the alkaline phosphatase. Both analyzers employ a photon counter to read the results, which are then converted to mg/L results

Differences		
Item	Device	Predicate
Intended use	For the quantitative measurement of CRP in human serum and plasma and with whole blood samples.	For the quantitative measurement of CRP in human serum and plasma.
Capture	Magnetic particles	Beads
Traceability	CRM 470	WHO 1st International Standard 85/506 from which CRM 470 transferred
Controls	Not included	Included

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

- NCCLS Evaluation of the Linearity of Quantitative Measurement Procedures; A Statistical Approach, Approved Guideline ISBN 1-56238-498-8.
- ISO 14971:2000 Medical Devices application of Risk Management to Medical Devices.
- ISO 17511:2003(E) In Vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials.
- NCCLS How to define and determine reference intervals in the clinical laboratory C28-A2 [ISBN 1-56238-406-6]
- NCCLS Method comparison and bias estimation using patient samples EP9-A2: [ISBN 1-56238-472-4]
- NCCLS Protocols for determination of limits of detection and limits of quantitation EP17-A [ISBN 1-56238-551-8]
- NCCLS Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline Second Edition NCCLS Document EP5-A2 [ISBN 1-56238-542-9]
- NCCLS Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline Second Edition NCCLS Document EP6-A [ISBN 1-56238-542-9]

L. Test Principle:

In the PATHFAST hsCRP procedure, alkaline phosphatase labeled anti CRP monoclonal antibody and anti CRP monoclonal antibody coated magnetic particles are mixed with sample. CRP contained in the specimen binds to the CRP antibodies forming an immunocomplex with enzyme labeled antibody and antibody coated magnetic particles. After removing the unbound enzyme labeled antibody, a chemiluminescent substrate is added to the immunocomplex. After a short incubation, the luminescence generated by enzyme reaction is detected. The CRP concentration in the specimen is calculated by means of a standard curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
 - a. *Precision/Reproducibility:*

Intrassay precision was assessed with serum and Li-heparinized plasma and whole blood samples at three levels of the test. Because the PATHFAST® analyzer runs only six samples with each run, each sample was tested twenty consecutive times.

Data from intra-assay precision for hsCRP with serum samples

N=20	Level 1	Level 2	Level 3
Mean (mg/L)	0.910	8.99	13.6
SD	0.047	0.364	0.688
%CV	5.1%	4.1%	5.1%
Minimum	0.804	8.19	11.8
Maximum	1.00	9.55	14.6
Range	0.196	1.36	2.80

Data from intra-assay precision for hsCRP with Li-heparinized plasma samples

N=20	Level 1	Level 2	Level 3
Mean (mg/L)	1.29	7.24	13.0
SD	0.068	0.290	0.485
%CV	5.3%	4.0%	3.7%
Minimum	1.17	6.87	11.5
Maximum	1.44	7.85	13.9
Range	0.270	0.980	2.40

Data from intra-assay precision for hsCRP with Li-heparinized whole blood samples

N=20	Level 1	Level 2	Level 3
Mean (mg/L)	1.33	7.99	14.5
SD	0.064	0.417	0.902
%CV	4.8%	5.2%	6.2%
Minimum	1.22	7.13	12.9
Maximum	1.41	8.77	16.4
Range	0.190	1.64	3.50

Inter-assay precision was assessed with serum and Li-heparinized plasma samples at three or four levels of the test range. Samples were tested in duplicate over 20 days, with two runs per day.

Data for hsCRP Inter-assay precision testing, serum

Level 1 mean - 0.916	SD	%CV
Within-run precision	0.069	7.5
Total precision	0.068	7.4
Level 2 mean - 4.63		
Within-run precision	0.279	6.0
Total precision	0.374	8.1
Level 3 mean - 15.1		
Within-run precision	1.19	7.8
Total precision	1.29	8.5
Level 4 mean - 25.6		
Within-run precision	1.24	4.8
Total precision	1.40	5.3

Data for hsCRP Inter-assay precision testing, plasma

Level 1 mean - 0.895	SD	%CV
Within-run precision	0.064	7.1
Total precision	0.069	7.7
Level 2 mean - 11.1		
Within-run precision	0.921	8.3
Total precision	0.909	8.2

Level 3 mean - 27.2		
Within-run precision	1.82	6.7
Total precision	2.16	7.9

b. *Linearity/assay reportable range:*

A dilution series was prepared by mixing non-CRP serum with human serum containing CRP to several levels of the test. A second dilution series was prepared by mixing Li-heparinized plasma containing CRP with saline diluent to several levels of the test. The diluted samples were tested in triplicate on the PATHFAST® analyzer. The mean of the measured concentration at each level was compared with the expected concentration based on the dilution level and the linear fit was assessed. The linearity claim is based on a percent deviation of < 10% at the two highest analyte concentrations. The assay range is from 0.05 to 30.0 mg/L

Serum Samples	Theoretical value	Actual Mean	Deviation from Theoretical	% Deviation	% Recovery
Level 10 (mg/L)	32.0	32.0	0.000	0.0%	100.0%
Level 9 (mg/L)	28.8	28.0	-0.800	-2.8%	97.2%
Level 8 (mg/L)	25.6	27.6	1.967	7.7%	107.7%
Level 7 (mg/L)	22.4	23.4	1.000	4.5%	104.5%
Level 6 (mg/L)	19.2	18.9	-0.267	-1.4%	98.6%
Level 5 (mg/L)	16.0	16.4	0.367	2.3%	102.3%
Level 4 (mg/L)	12.8	14.1	1.267	9.9%	109.9%
Level 3 (mg/L)	9.60	9.15	-0.447	-4.7%	95.3%
Level 2 (mg/L)	6.40	6.69	0.287	4.5%	104.5%
Level 1 (mg/L)	3.20	3.17	-0.030	-0.9%	99.1%
Diluent	0	0.000	0.000	-	-
$y = 0.985x - 0.062$ $r^2 = 0.994$					
Plasma Samples					
Level 10 (mg/L)	35.0	35.0	0.000	0.0%	100.0%
Level 9 (mg/L)	31.5	30.3	-1.20	-3.8%	96.2%
Level 8 (mg/L)	28.0	27.4	-0.593	-2.1%	97.9%

Serum Samples	Theoretical value	Actual Mean	Deviation from Theoretical	% Deviation	% Recovery
Level 7 (mg/L)	24.5	23.0	-1.49	-6.1%	93.9%
Level 6 (mg/L)	21.0	19.6	-1.39	-6.6%	93.4%
Level 5 (mg/L)	17.5	16.6	-0.883	-5.0%	95.0%
Level 4 (mg/L)	14.0	12.7	-1.28	-9.1%	90.9%
Level 3 (mg/L)	10.5	9.56	-0.950	-9.0%	91.0%
Level 2 (mg/L)	7.01	6.31	-0.700	-10.0%	90.0%
Level 1 (mg/L)	3.50	3.35	-0.153	-4.4%	95.6%
Diluent	0	0.000	0.000	-	-
$y = 1.011x + 0.601$ $r^2 = 0.998$					

The test was also evaluated for linearity at the lower end of the test range. Dilution series were prepared as before using normal plasma and serum and plasma samples containing CRP. The samples were tested in triplicate on the PATHFAST® analyzer.

Serum Samples	Theoretical value	Actual Mean	Deviation from Theoretical	% Deviation	% Recovery
Level 10 (mg/L)	0.354	0.354	0.000	0.0%	100.0%
Level 9 (mg/L)	0.319	0.291	-0.028	-8.8%	91.2%
Level 8 (mg/L)	0.283	0.291	0.008	2.9%	102.9%
Level 7 (mg/L)	0.248	0.228	-0.020	-8.1%	91.9%
Level 6 (mg/L)	0.213	0.220	0.007	3.3%	103.3%
Level 5 (mg/L)	0.177	0.178	0.001	0.8%	100.8%
Level 4 (mg/L)	0.142	0.148	0.006	4.5%	104.5%
Level 3 (mg/L)	0.106	0.107	0.001	1.3%	101.3%
Level 2 (mg/L)	0.071	0.066	-0.005	-7.0%	93.0%
Level 1 (mg/L)	0.035	0.035	0.000	0.0%	100.0%
Diluent	0	0	0.000	-	-

	y = 1.021x-0.001 r2 =0.991				
Plasma Samples					
Level 10 (mg/L)	0.353	0.353	0.000	0.0%	100.0%
Level 9 (mg/L)	0.317	0.339	0.021	6.7%	106.7%
Level 8 (mg/L)	0.282	0.286	0.004	1.5%	101.5%
Level 7 (mg/L)	0.247	0.256	0.009	3.6%	103.6%
Level 6 (mg/L)	0.212	0.213	0.002	0.8%	100.8%
Level 5 (mg/L)	0.176	0.175	-0.001	-0.6%	99.4%
Level 4 (mg/L)	0.141	0.141	0.000	0.2%	100.2%
Level 3 (mg/L)	0.106	0.106	0.000	0.2%	100.2%
Level 2 (mg/L)	0.071	0.070	-0.001	-1.2%	98.8%
Level 1 (mg/L)	0.035	0.033	-0.002	-6.4%	93.6%
Diluent	0.000	0.000	0.000	-	-
	y = 0.965x+0.003 r2 =0.998				

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
 The calibrators for PATHFAST hsCRP are traceable to the reference material CRM 470 and stability is based on real time studies.

d. *Detection limit:*

Limit of Blank

Normal serum samples with CRP removed were tested 60 consecutive times with the PATHFAST® hsCRP test. The limit of blank was calculated from the results based on NCCLS EP17-A.

$$\text{LoB} = 0.0004 + 1.65 * 0.0005 = 0.001 \text{ mg/L}$$

Limit of Detection/Limit of Quantitation

Five serum samples spiked with CRP calibrator to very low levels of the test were tested in replicates of five over four days. The results were evaluated to determine the limit of detection and the limit of quantitation.

$$\text{LoD} = 0.001 + [1.645 / (1 - 1 / (4 \times 100))] \times 0.001 = 0.002$$

The limit of quantitation, or level above which the %CV was ≤10%, was 0.008 mg/L

e. *Analytical specificity:*

Two levels of samples were tested on the PATHFAST® analyzer. The measurement obtained was compared to the expected value, which is the value of the serum samples with no interfering substances added. The results are shown in the following table:

Interferent	Interferent concentration	Level 1		Level 2	
		Results (mg/L)	% recovery	results (mg/L)	% recovery
Bilirubin conjugated (mg/dL)	0	1.97	100.0%	25.1	100.0%
	12	1.92	97.5%	24.9	99.3%
	24	2.10	106.3%	26.5	105.6%
	36	1.93	98.0%	25.0	99.6%
	48	1.97	100.0%	24.6	98.3%
	60	1.89	95.8%	27.1	108.1%
Bilirubin free (mg/dL)	0	1.82	100.0%	25.5	100.0%
	12	1.98	109.0%	24.7	96.9%
	24	1.87	102.9%	26.8	105.2%
	36	1.80	98.9%	24.3	95.3%
	48	1.89	103.8%	24.1	94.4%
	60	1.73	95.2%	26.0	102.0%
Hemoglobin (mg/dL)	0	1.79	100.0%	24.5	100.0%
	200	1.87	104.3%	24.4	99.7%
	400	1.87	104.3%	24.8	101.2%
	600	1.69	94.6%	23.3	95.1%
	800	1.80	100.7%	22.8	93.1%
	1000	1.87	104.5%	24.2	98.8%
Lipemia	0	1.89	100.0%	25.2	100.0%
	1000	1.92	101.6%	25.4	100.7%
	2000	1.90	100.4%	25.7	102.1%
	3000	1.85	97.9%	24.3	96.6%
	4000	1.93	102.3%	26.5	105.0%
	5000	2.06	109.0%	26.8	106.5%
Rheumatoid factor (IU/mL)	0	1.90	100.0%	25.3	100.0%
	110	2.01	105.8%	24.4	96.4%
	220	1.79	94.4%	24.3	96.0%
	330	1.86	97.7%	26.2	103.8%
	440	1.97	103.9%	26.3	104.1%
	550	2.03	106.8%	25.0	98.8%

Triglyceride (mg/dL)	0	1.99	100.0%	25.7	100.0%
	200	1.94	97.7%	26.5	102.8%
	400	1.82	91.3%	26.4	102.5%
	600	1.84	92.6%	26.3	102.2%
	800	1.97	98.8%	27.3	106.2%
	1000	2.08	104.7%	26.9	104.4%

f. Assay cut-off:

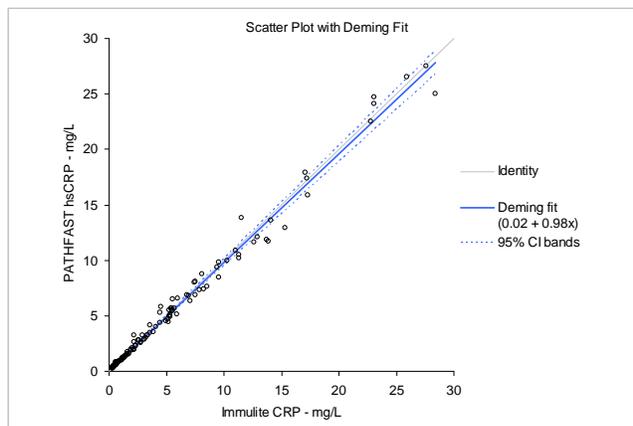
Not applicable

2. Comparison studies:

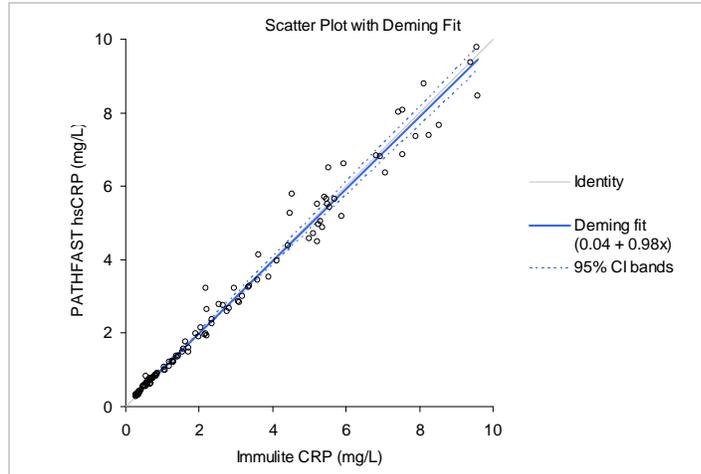
a. *Method comparison with predicate device:*

229 serum samples collected from patients with inflammatory disorders were tested with the PATHFAST® hsCRP test and the IMMULITE® hsCRP test. The hsCRP concentration of the samples ranged from 0.268 to 144 mg/L with the IMMULITE® hsCRP test. In the PATHFAST hsCRP assay, 90 samples above 30.0 mg/L of CRP were not included in the analysis, leaving 139 samples. There were 119 results below 10. The results of the study are presented below.

$y = 0.98x + 0.024$; $r = 0.995$; $n = 139$
 Range of samples: 0.268 -28.4 mg/L



$y = 0.98x + 0.037$; $r = 0.991$; $n = 119$
 Range of samples: 0.268 -9.58 mg/L



b. *Matrix comparison:*

A study using different matrices was performed using whole blood samples collected in plain tubes, lithium heparin, sodium heparin and EDTA-2K and EDTA-2Na tubes. Lithium heparin was compared to serum, and the various whole blood samples were compared to plasma. Samples were spiked to obtain high values. The samples ranged from 0.05 to 28.0 mg/L. The correlations obtained between lithium heparin plasma and other sample matrices are presented below.

$$y = 0.99x + 0.333, r = 0.990, n = 48$$

(y: lithium heparin plasma; x: serum)

$$y = 0.98x - 0.213, r = 0.996, n = 49$$

(y: lithium heparin whole blood; x: lithium heparin plasma)

$$y = 1.03x - 0.025, r = 0.991, n = 65$$

(y: sodium heparin plasma; x: lithium heparin plasma)

$$y = 0.97x - 0.034, r = 0.994, n = 54$$

(y: sodium heparin whole blood; x: lithium heparin plasma)

$$y = 0.98x - 0.217, r = 0.993, n = 56$$

(y: EDTA-2K plasma; x: lithium heparin plasma)

$$y = 1.02x - 0.235, r = 0.995, n = 48$$

(y: EDTA-2K whole blood; x: lithium heparin plasma)

$$y = 0.98x - 0.233, r = 0.992, n = 49$$

(y: EDTA-2Na plasma; x: lithium heparin plasma)

$$y = 0.95x + 0.143, r = 0.987, n = 53$$

(y: EDTA-2Na whole blood; x: lithium heparin plasma)

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):
 Testing with the PATHFAST® hsCRP Test was performed in three point of care sites. Operators were trained on the use of the PATHFAST® analyzer and testing the PATHFAST® reagents using the PATHFAST® Operator’s Manual and draft package inserts.

The PATHFAST® analyzer was calibrated at each site by an operator before testing was initiated.

The following studies were performed at each site:

- Precision testing at 2 levels of the test
- Precision testing of whole blood samples
- Comparison with predicate method

Testing was performed at each site over five days. Two operators performed the testing at each site.

Precision testing

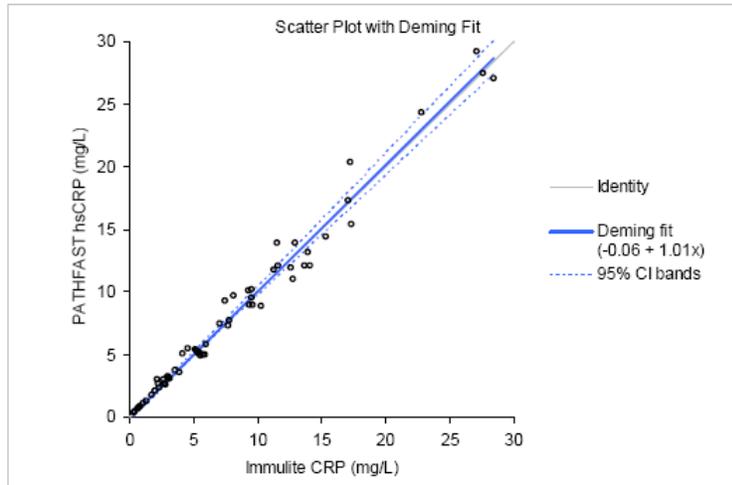
Two levels of control samples were tested in duplicate daily for five days.

	Site	Mean	SD	%CV
Level 1	Site 1	0.711	0.029	4.1%
	Site 2	0.670	0.041	6.1%
	Site 3	0.710	0.041	5.8%
	Overall	0.697	0.043	6.2%
Level 2	Site 1	7.23	0.367	5.1%
	Site 2	6.57	0.412	6.3%
	Site 3	6.76	0.470	7.0%
	Overall	6.85	0.514	7.5%

Lithium heparin whole blood samples were tested in duplicate. At least ten samples were tested at each site, %CV ranged from 0.3% to 8.8%.

Method comparison testing

Sixty serum samples ranging from 0.33 to 28.4 mg/L, previously tested with the predicate method were analyzed using the PATHFAST® hsCRP test. Twenty samples were tested at each site. Results of PATHFAST® testing were analyzed by Deming regression. The slope of the regression line was 1.01 the intercept was -0.056 r = 0.990.



4. Clinical cut-off:
Not Applicable

5. Expected values/Reference range:
Using the PATHFAST® hsCRP assay, the calculated value for the 97.5th percentile for CRP in serum samples of 275 apparently healthy individuals (160 males and 115 female – age range 16-77 years) was 4.16 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.