

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

A. 510(k) Number:

k091052

B. Purpose for Submission:

Device modification: addition of conventional CRP to previously cleared Piccolo xpress™ Panel of 8 chemistry analytes

C. Measurand:

C-reactive protein, conventional

D. Type of Test:

Quantitative

E. Applicant:

ABAXIS INC.

F. Proprietary and Established Names:

Piccolo® C-Reactive Protein (CRP) Test System

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:
The Piccolo® C-Reactive Protein Test System used with the Piccolo xpress™ Chemistry Analyzer is intended to be used for the *in vitro* quantitative determination of CRP concentration in lithium heparinized whole blood, lithium heparinized plasma, or serum, in a clinical laboratory setting or point-of-care location. This test is not intended for high sensitivity CRP measurement.
2. Indication(s) for use:
C-reactive Protein test results aid in the evaluation of infection, tissue injury, and inflammatory disorders in conjunction with other laboratory and clinical findings.
3. Special conditions for use statement(s):
For prescription use only. Not intended for high sensitivity CRP measurements.
4. Special instrument requirements:
Piccolo xpress™ Chemistry Analyzer (k934592)

I. Device Description:

Each Piccolo MetLyte Plus CRP Reagent Disc contains dry test-specific reagent beads: 67.2 µg Anti-human CRP coated latex (mouse) and 0.3 µg Anti-human CRP (goat). A dry sample blank reagent (comprised of buffer, surfactants, excipients and preservatives) is included in each disc for use in calculating concentrations of CRP and chemistry analytes. Each disc also contains a diluent consisting of surfactants and preservatives.

The discs are designed to separate a heparinized whole blood sample into plasma and blood cells. The disc meters the required quantity of sample and diluent, then mixes the plasma sample with the diluent and delivers the mixture to the reaction cuvette contained in the disc perimeter. The diluted sample mixes with the reagent beads initiating the chemical reactions that are then monitored by the analyzer. The discs are 8 cm in diameter and are single-use devices. The disc may also be used with serum.

(The Abaxis Piccolo System is an established point of care device since 1994 with eight cleared Chemistry analytes: Blood Urea Nitrogen (k942782); Chloride (k010670); Creatinine Kinase (k992140); Creatinine (k942782); Glucose (k934592); Potassium (k992140); Sodium (k993211); and Total Carbon Dioxide (k992149).

J. Substantial Equivalence Information:

1. Predicate device name(s):
Synchron® Systems High Sensitivity Cardiac C-Reactive Protein (CRPH)
2. Predicate K number(s):
K070626
3. Comparison with predicates:

Difference		
Item	New Device	Predicate Device
Intended use	For quantitative determination of C-Reactive Protein in serum or lithium heparinized whole blood or plasma in conjunction with Piccolo xpress Chemistry analyzer in a clinical laboratory setting or point-of-care location. This test is not intended for high sensitivity CRP measurement.	For quantitative determination of High Sensitivity Cardiac C-Reactive Protein in human serum or plasma in conjunction with Synchron LX®20 PRO System, UniCel® DxC 600/800 System(s), and Synchron® Systems CAL 5 Plus.
Methodology	Enhanced latex-agglutination turbidimetric immunoassay	Rate turbidimetry
Sample matrices	Serum, heparinized whole blood and plasma samples (lithium heparin)	Serum and plasma samples (EDTA, lithium heparin, sodium heparin)
Sample size	Approximately 10 µL	20 µL (12 µL ORDAC*)
Calibration	Bar code with factory calibrated lot for specific data	Single point adjusted, pre-determined calibration curve
Reagents	Dry test-specific reagent beads and liquid diluent;	Liquid reagents Active ingredients: Anti-CRP

Difference		
Item	New Device	Predicate Device
	reconstitution performed by analyzer. Active ingredients: Anti-CRP antibody-coated latex particles (latex particle-bound mouse monoclonal anti-CRP antibody) and Anti-CRP goat antibody	antibody-coated particles (particle-bound goat and mouse anti-CRP antibody)
Assay ranges	5.0 – 200.0 mg/L	0.2 – 80.0 mg/L (60 – 380 mg/L ORDAC*)
Reference Intervals	<7.5 mg/L	<0.748 mg/dL

* Beckman LX 20 has an Overrange Detection and Correction for samples that exceed the 80 mg/mL limit. This is an automated process within the analyzer that retests with a smaller sample volume.

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

Standard documents:

CLSI EP 17: Determination of limits of detection and limits of quantitation

CLSI EP 18: Quality management for unit-use testing.

L. Test Principle:

The method used by Abaxis is an enhanced latex-agglutination turbidimetric immunoassay. Sample is mixed with a suspension of mouse anti-human CRP monoclonal antibody that is bound to latex. CRP in the sample binds to the antibody-latex particles and agglutinates creating turbidity. Light scattering from the turbidity is used as a measure of CRP. Turbidity is measured as a change in absorbance at 630 nm. This absorbance change is directly proportional to the CRP in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility of the assay was assessed by testing in duplicate two levels of controls, one patient samples close to the 7.5 mg/L assay cut-off performed in two sites over 20 days (n=80). Additional four samples (two close to assay cut-off, one mid-range and one upper-range) were tested in duplicate at one site for five days (n=40). The intra-assay and inter-assay %CV ranges were from 1.7% to 8.4% and 2.9% to 9.8%, respectively (see tables below).

Sample	Mean (mg/L)	Intra-assay		Inter-assay	
		SD (mg/L)	%CV	SD (mg/L)	%CV
Control Level 1	33.0	1.21	3.7	2.12	6.4
Control Level 2	108.0	108.0	1.7	3.14	2.9
Sample #1	8.3	0.70	8.4	0.81	9.8
Sample #2	8.1	0.49	6.1	0.51	6.3

Sample #3	8.8	0.54	6.2	0.54	6.2
Sample #01	34.5	1.04	3.0	1.09	3.2
Sample #02	105.5	2.06	1.9	2.3	2.2

b. *Linearity/assay reportable range:*

Linearity across the assay measuring range (5.0 - 200 mg/L) was confirmed by testing pooled sera with low range concentration of 4.6 mg/L and pooled sera with high concentrations from 202.8 mg/L. Nine dilution pools were calculated and prepared with the low and high sample pools using the S=9 Dilution Scheme recommended in CLSI EP6-A standard Appendix A. The diluted samples were re-assayed four times on four Piccolo xpress Chemistry Analyzer.

Linearity results were as follows:

Regression Equation	N	Slope	Intercept	R ²	r
Y= 1.037x – 0.764	4	1.037	-0.764	0.994	0.997

Reportable range: 5.0 – 200.0 mg/L.

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

Traceability: The calibrators are traceable to Beckman’s method calibration to Standard Reference Material BCR 470

Stability: Accelerated stability testing 25°C and 35°C at 0, 14, 21, and 28 days and 0, 3, and 10 days testing intervals respectively. Real time testing at 2-8°C were tested at 0, 1, 3, 6, 9, 12, 15, 18 and 21 months. The reagent discs are stored at recommended temperature 2-8°C in their sealed pouches. Expiration date claim is 21 months.

d. *Detection limit:*

Limit of Blank (LoB) Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined using five pools including the lowest CRP calibrator (human serum spiked with CRP to 4.5 mg/L), three dilutions of lowest calibrators in saline, and a saline blank. Each pool was assayed twenty times, twice on each of 10 Piccolo xpress Chemistry analyzers.

The LoB is determined either by Gaussian or non-Gaussian distribution. If Gaussian, LoB is determined by equation; if non-Gaussian, it is determined as the non-parametric 95th percentile.

The LoD was determined by equation $LoD = LoB + (C \beta * SDs)$ where $C \beta = 1.645 / (1 - (1 / (4 * f)))$, where f is degrees of freedom (n=1), and SDs is the standard deviation of the observations.

The LoQ was determined as the lowest sample run that displayed CV < 20% and Accuracy vs. expected value of 80-120% (inaccuracy < 20%).

The results were as follows:

$$LoB = 0.32 \text{ mg/L}$$

$$LoD = 0.91 \text{ mg/L}$$

$$LoQ = 2.5 \text{ mg/L}$$

e. *Analytical specificity:*

Interference studies:

Endogenous substances : Six Human serum pools (28 and 250 mg/L CRP) and a control pool were tested with up to 750 mg/dL Hemoglobin, 35 mg/dL Bilirubin and 750 mg/dL Triglycerides) in four replicates on each of four Piccolo xpress Chemistry analyzers. Interference were observed at $\leq 10\%$. The Piccolo xpress Chemistry analyzer will automatically print ‘HEM’, ‘LIP’, or ‘ICT’ if interferents are above the physical interferent values as listed above.

Exogenous substances: Thirty five drugs and other substances were selected as potential interferents with the CRP methods based on recommendations by Young, DS Effects of drugs on laboratory testing 3rd Ed. Wash DC AACC Press 1990. Listing of exogenous and other substances and levels tested of CRP for each level with $\pm 10\%$ shift were as follows:

Potential Interferent	Highest Concentration Tested (mg/dL unless otherwise specified)
Acetaminophen	100
Acetoacetate	102
Acetylsalicylic Acid	50
Ampicillin	30
Ascorbic acid	3
Caffeine	10
Cephalothin (Keflin)	400
Chloramphenicol	100
Cimetidine	16
Dopamine	13
Epinephrine	1
Erythromycin	10
Glutathione	30
Hydrochlorothiazide	7.5
Ibuprofen	50
Isoniazide	4
Ketoprofen	50
L-dopa	5
Lidocaine	1
Lithium Lactate	84
Methicillin	100
Methotrexate	0.5
Metronidazole	5
Nafcillin	1
Nitrofurantoin	20
Oxacillin	1
Oxaloacetate	132
Penicillin G	100
Phenytoin (5,5-Diphenylhydantion)	3
Proline	4
Rifampin	0.5
Salicylic Acid	50
Sulfadiazine	150
Sulfanilamide	50
Theophylline	20

Substances tested with significant $>10\%$ shift were as follows:

	Concentration Which Produces > 10% Interference	% Interference ^A Observed
C-Reactive Protein		
Glutathione	30	13% dec.
Isoniazide	4	16% dec.
L-dopa	5	28% dec.
Oxaloacetate	132	57% dec.

Rheumatoid factor (RF): Undiluted and Normal serum samples were spiked ~150 mg/L CRP were tested with RF serum (up to 644 IU/mL). Each sample was run in quadruplicate on four Piccolo analyzers. No interference were observed.

HAMA interference: Undiluted and Normal serum samples were spiked 50 mg/L CRP were tested with a known HAMA serum (up to 115ng/mL from ProMedDx). Each sample was run in quadruplicate on four Piccolo analyzers. No interference were observed.

The Package Insert states “Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain HAMA”.

These interferent listings and results as shown above are listed in the CRP Package Insert.

High dose effect: A commercial CRP calibrator with an assigned value of 1,040 mg/L was run neat and diluted into a serum pool to obtain CRP at 520 and 260 mg/L. Each sample was assayed four times on four Piccolo analyzers. No high dose effect (prozone effect) was observed.

The extremely high CRP concentrations up to 1,000 mg/L would not be expected to provide numbers within the Abaxis dynamic ranges. An error code stating >200 mg/L will flag the results.

f. Assay cut-off:

Assay cut-off: <7.5 mg/L. The assay cut-off was determined from 69 healthy adults tested in duplicate by the Abaxis CRP method and the Beckman CRP method. CRP Reference interval was based on demonstrated transferability of the reference intervals from Beckman reference interval (per CLSI EP5-A guideline).

2. Comparison studies:

a. Method comparison with predicate device:

The method comparison study was performed on 113 samples with concentrations ranging from 5.0 – 200.0 mg/L. Of the 113 samples, 20 samples were from 5-10 mg/L ranges; 29 samples from 10.1-25 mg/L ranges; 12 samples from 25.1-55.0 mg/L ranges; 13 samples from 55.1-89 mg/L ranges; 12 samples from 89.1-133 mg/L ranges; 10 samples from 133.1-180 mg/L ranges; 7 samples from 180.1-187 mg/L ranges; 10 samples from 187.1-

200 mg/L ranges. The regression analysis were as follows:

Regression Equation	N	Slope	95% CI	Intercept	95% CI	R ²	r
Y= 0.990x – 0.4	113	0.990	0.974 – 1.006	-0.4	-1.1 to 0.3	0.996	0.998

b. *Matrix comparison:*

Y axis	X axis	N	Slope	Intercept	R ²
Lithium heparinized plasma	Lithium heparinized whole blood	48	0.995	0.2	1.000
Serum	Lithium heparinized whole blood	57	1.005	0.5	0.999
Serum	Lithium heparinized plasma	57	1.010	0.3	0.999

3. Clinical studies:

a. Clinical Sensitivity and specificity:

Not applicable

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

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Less than 7.5 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.