510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K161982

B. Purpose for Submission:

New Device

C. Measurand:

C-Reactive Protein

D. Type of Test:

Turbidimetry, Quantitative

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

C-Reactive Protein Kit for use on SPA_{PLUS}

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.5270 –

2. Classification:

   Class II

3. Product code:

   DCN – System, Test, C-Reactive Protein

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use:

   The C-Reactive Protein Kit for use on SPAPLUS is intended for the quantitative in vitro determination of C-reactive protein (CRP) concentration in serum. Measurement of C-reactive protein aids in evaluation of the amount of injury to body tissues and for evaluation of infection, tissue injury, and inflammatory disorders. This product is suitable for use on the SPAPLUS analyzer.

2. Indication for use:

   Same as Intended Use

3. Special conditions for use statement:

   For prescription use only

4. Special instrument requirements:

   The Binding Site SPAPLUS analyzer (K040958)

I. Device Description:

The C-Reactive Protein Kit for use on SPA_{PLUS} is comprised of the following reagents:

- Antiserum: Supplied in stabilized liquid form. Preservatives: 0.099% sodium azide, TRIS pH 8.0.
- Calibrator and Controls: Pooled human serum, supplied in stabilized liquid form. Containing 0.099% sodium azide, as preservative. The concentration given on the quality control certificate has been obtained by comparison with the ERM-DA474 international reference material.
- Reaction Buffer: Containing 0.099% sodium azide, TRIS pH 7.5 as preservatives.

J. Substantial Equivalence Information:

1. Predicate device name:

   Roche Diagnostics Tina-Quant C-Reactive Protein Gen 3

2. 510(k) number:

   K083444

3. Comparison with predicate:

Similarities		
Item	Device C-Reactive Protein Kit for use on SPA_{PLUS}	Predicate Tina-Quant C-Reactive Protein Gen 3
Intended Use/ Indication for Use	The C-Reactive Protein Kit for use on SPAPLUS is intended for the quantitative in vitro determination of C-reactive protein (CRP) concentration in serum. Measurement of C-reactive protein aids in evaluation of the amount of injury to body tissues and for evaluation of infection, tissue injury, and inflammatory disorders. This product is suitable for use on the SPAPLUS analyzer.	Immunoturbidimetric assay for the in vitro quantitative determination of CRP in human serum and plasma on Roche automated clinical chemistry analyzers. Measurement of C-Reactive protein aids in the evaluation of the amount of injury to body tissues.
Measurement	Quantitative	Same
Method	Turbidimetry	Same
Reference Interval	< 5 mg/L	Same

Differences		
Item	Device: C-Reactive Protein Kit for use on SPA_{PLUS}	Predicate: Tina-Quant C-Reactive Protein Gen 3
Instrument	SPAPLUS analyzer	Hitachi 912, 917, Modular P
Antibody	Goat anti-human CRP	Mouse anti-human CRP
Sample type	Serum	Serum, Li-heparin plasma, and EDTA plasma
Reagent	Antiserum	Latex particles coated with mouse anti-CRP
Calibration	5-point calibrator set	5-point, single calibrator diluted on analyzer
Assay Measuring Range (AMR)	5–250 mg/L (neat) 50–2500 (1/10 dilution)	0.3–350 mg/L 0.6–700 mg/L (1/2 dilution)
Traceability	ERM-DA474	CRM470
Wavelength	340 nm	570 nm/800 nm

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

- Guidance for Industry - Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays
- EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures, Approved Guideline, Third Edition.

- EP6-A, Evaluation of Linearity of Quantitative Measurement, Approved Guideline, Second Edition.
- EP07-A2, Interference Testing in Clinical Chemistry, Approved Guideline, Second Edition
- EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline, Second Edition

L. Test Principle:

The determination of soluble antigen (CRP) concentration by turbidimetric methods involves the reaction with specific antiserum (anti-CRP) to form insoluble complexes. When light is passed through the suspension formed, a portion of the light is transmitted and focused onto a photodiode by an optical lens system. The amount of transmitted light is indirectly proportional to the specific protein concentration in the test sample. Concentrations are automatically calculated by reference to a calibration curve stored within the instrument.

M. Performance Characteristics:

1. Analytical performance: All results for analytical performance met the sponsor's pre-determined acceptance criteria for each study.

   a. Precision/Reproducibility:

   The precision and reproducibility of the assay was evaluated by testing four serum samples containing various concentrations of CRP. Each sample was run in duplicate, two runs per day, for 21 days with one lot of reagents on three SPAPLUS analyzers (n = 84 replicates per sample). The results are summarized in the table below.

Sample	Mean (mg/L)	Within-Run		Between-Run		Between-Day		Between-Instrument		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	6.03	0.11	1.9	0.27	4.5	0.41	6.9	0.34	5.6	0.51	8.4
2	8.64	0.11	1.3	0.33	3.8	0.50	5.8	0.53	6.1	0.61	7.1
3	21.34	0.13	0.6	0.41	1.9	0.31	1.5	0.04	0.2	0.53	2.5
4	65.17	0.30	0.5	1.16	1.8	0.00	0.0	0.43	0.7	1.20	1.8

The lot-to-lot reproducibility of the assay was evaluated by testing five serum samples containing various concentrations of CRP. Each sample was run in duplicate, two runs per day, for 21 days using three reagent lots on four SPAPLUS analyzers (n = 84 replicates per sample). The results are summarized in the table:

Sample	Mean (mg/L)	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	8.67	0.31	3.5	0.20	2.3	0.57	6.6	0.41	4.7	0.68	7.8
2	13.54	0.44	3.3	0.34	2.5	0.52	3.9	0.28	2.1	0.77	5.7
3	59.96	0.73	1.2	0.43	0.7	1.29	2.1	0.50	0.8	1.54	2.6
4	147.00	2.37	1.6	1.89	1.3	4.40	3.0	5.28	3.6	5.34	3.6
5	225.24	5.47	2.4	2.90	1.3	12.59	5.6	14.67	6.5	14.03	6.2

b. *Linearity/assay reportable range:*

Linearity: Linearity was evaluated according to the CLSI guideline EP6-A. A pooled serum sample containing a high concentration of CRP was mixed with normal serum to generate a series of 13 dilution samples. Each sample was tested in triplicate using one lot of reagent. The results of weighted regression analysis are summarized as follows:

Dilution Range (mg/L)	Slope (95% CI)	Y-intercept (95% CI)	R^2	% Recovery
2.80–315.33	1.00 (0.96–1.04)	−0.02 (−0.32–0.27)	1.00	−5.7%–7.4%

The manufacturer is reporting that the assay is linear from 5–250 mg/L.

Hook effect (antigen excess):

To evaluate the effect of antigen excess, a study was performed by testing a sample containing CRP concentration above the upper limit of the reportable range of the device. The obtained antigen excess capacity of the CRP kit for use on SPAPLUS is up to 3433 mg/L at the 1/10 dilution. The samples with analyte levels more than 10% above the upper limit of measuring range were flagged as antigen excess samples by the SPA_{PLUS} analyzer.

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

Traceability:

The calibrators used to calibrate the assay are traceable to the ERM-DA474 reference material.

Value assignment: The antiserum, calibrators and controls used in the CRP kit for use on SPAPLUS are purchased from DiaSys Diagnostic Systems GmbH. The antiserum is supplied in bulk form. The calibrators and controls are supplied in dispensed unlabeled vials. The Certificate of Analysis (COA) contains the assigned value for the controls and calibrators. Using the calibrator and control assigned

values from the COA, three curves are calibrated on the SPAPLUS analyzer and validated by comparing against the specification of tested kit. The controls are also run against each of the three calibration curves. The tested values must be within ±8.5% of the assigned value.

Stability:

The real-time stability for un-opened (shelf life), open-vial, and on-board stability studies were each performed using multiple lots of kit reagent pack, calibrators and controls. The results support the following stability claims:

Kit Reagent Pack	Un-opened	5 months at 2–8°C
	Open-vial	3 months at 2–8°C
	On-board	30 days at 8–12°C
Calibrators/Controls	Un-opened	5 months at 2–8°C
	Open-vial	3 months at 2–8°C

d. Detection limit:

Limit of Blank (LoB) was determined by assaying one analyte-depleted serum sample with one lot of reagent to generate sixty data points. LoB was calculated as the 95th percentile using the non-parametric method. The claimed LoB is 0.5 mg/L.

The Limit of Detection (LoD) was determined by assaying five samples with CRP concentration close to the lower limit of reportable range. Each sample was tested in replicates of 12 over five days with two reagent lots. The LoD was calculated as the LoB + 1.645 x SD of the replicates for the low level samples. The LoD was determined as 0.75 mg/L and 0.72 mg/L for each lot. The claimed LoD is 0.75 mg/L.

The Limit of Quantification (LoQ) was validated by testing four samples with CRP concentration close to the lower limit of reportable range. Each sample was tested in replicates of five over three days with two reagent lots. The LoQ was verified to be the value that meets the accuracy goal of 20% CV of within-lab precision. The result supports that the claimed LoQ is 5 mg/L which is the lower limit of the measuring range claimed for the assay.

e. Analytical specificity:

Endogenous Interference: Three serum samples (7.74, 61.42, and 144.67 mg/L) were spiked with endogenous interferents respectively. The control samples were prepared for each interfering substance by spiking with the same volume of diluents. Each sample was tested in triplicates and the percent difference was calculated by comparing to a corresponding control sample. No interference was detected in the samples up to the concentrations listed in the table below.

Potential Interfering Substances	Maximum Concentration	Range of % Difference
Unconjugated Bilirubin	200 mg/L	−7.50– −4.32
Hemoglobin	5 g/L	−5.24–0.28
Intralipid	250mg/dL	−1.42–0.20
Rheumatoid Factor	4834 IU/mL	6.14–6.69 *
	2417 IU/mL	−3.08% **

* For samples with CRP concentration at 61.42 and 144.67 mg/L
** For sample with CRP concentration at 7.74 mg/L

Drug Interference: The same protocol used for evaluation of endogenous interference was used to evaluate the potential interference of common drugs. No interference was observed for each drug at the concentrations listed below.

Name of Agent	Concentration Tested
Acetaminophen	1324µmol/L
Acetylsalicylic Acid	1.95mmol/L
Amoxicillin	206µmol/L
Ascorbic Acid	342µmol/L
Caffeine	308µmol/L
Cefotaxime	673µmol/L
Theophylline	222µmol/L
Chloramphenicol	155µmol/L
Cimetidine	79.2µmol/L
Digoxin	7.8nmol/L
Fluconazole	245µmol/L
Ibuprofen	606.25µmol/L
Penicillin	75mg/L
Phenytoin	198µmol/L

f. Assay cut-off:

See the reference range/expected value.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 225 samples including 82 samples from healthy blood donors and 143 samples from hospital patients samples were tested with the CRP Kit for use on SPAPLUS and the predicate device Tina-Quant CRP Gen 3. Among 225 samples, 144 samples had CRP concentration within the measuring ranges of both assays. The Passing-Bablok regression analysis was performed by comparing the results obtained from the CRP Kit for use on SPAPLUS (y) and the predicate (x). The results are summarized below:

N	Range (mg/L)	Slope (95% CI)	Intercept (95% CI)	Correlation Coefficient
144	5.40–499.60	1.02 (1.01–1.04)	3.22 (2.32–4.27)	1.00

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity and Clinical Specificity:

Not applicable

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

Not applicable

4. Clinical cut-off

See assay cut-off.

5. Expected values/Reference range:

The reference range is < 5 mg/L in apparently healthy individuals (*Dati F, et al. 1996, Consensus of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in serum based on the standardization against the IFCC/BCR/CAP reference material (CRM 470). Eur J. Clin Chem Clin Biochem.34:517-520*).

The reference range in the normal population was verified per CLSI c28-A3c by testing 22 apparently healthy individuals using the CRP Kit for use on SPAPLUS. The results showed that one sample had a CRP concentration at 5.2 mg/L and the remaining samples (95.5%) had a CRP concentration < 5mg/L using the CRP Kit for use on SPAPLUS. It is recommended that each laboratory should establish its own reference range for the population in its region.

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.