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

A. 510(k) Number

k180099

B. Purpose for Submission:

New Device

C. Measurand:

High Sensitivity C-Reactive Protein

D. Type of Test:

Quantitative Immunoturbidimetry Assay

E. Applicant:

The Binding Site Group Ltd.

F. Proprietary and Established Names:

Optilite® High Sensitivity C-Reactive Protein Kit

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DCN	II	866.5270, C-reactive protein immunological test system	82- Immunology

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

The Optilite High Sensitivity C-Reactive Protein Kit is intended for the quantitative in vitro measurement of C-Reactive Protein in serum using the Binding Site Optilite analyser for evaluation of conditions thought to be associated with inflammation, in otherwise healthy individuals. This test should be used in conjunction with other laboratory and clinical findings.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

The Binding Site Optilite analyser

I. Device Description:

The Optilite High Sensitivity C-Reactive Protein Kit consists of the following: latex reagent, single calibrator, controls (high and low) and reaction buffer in liquid form. The reagents contain 0.099% sodium azide as preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) numbers:

C-Reactive Protein High Sensitive Test System for Cobas Integra Instruments, k053603.

2. Comparison with predicate:

Item	Candidate Device: Optilite® High Sensitivity C-Reactive Protein Kit on the Binding Site Optilite analyzer	Predicate Device: C-Reactive Protein High Sensitive Test System for Cobas Integra Instruments (k053603)
Similarities		
Intended Use	Quantitative in vitro measurement of C-reactive protein (CRP)	Same
Reagent Type	Latex enhanced	Same
Differences		
Measuring range	0.5-10mg/L	0.1-20.0mg/L 1.5-300mg/L (1/15 dilution)
Analyzer	Optilite	Integra
Traceability	DA474	ERM-DA470 (CRM470)

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 Guidance for Industry and FDA Staff.

Clinical and Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline-Third Edition.

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition.

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline.

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 (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   The precision studies were performed following the recommendations in the CLSI EP05-A3 guideline. The precision samples consisted of 5 serum samples at the following concentrations: 0.863 mg/L, 1.65 mg/L, 3.02 mg/L, 5.06 mg/L and 8.54 mg/L. The samples were run in duplicate with 2 runs per day, using one instruments and one reagent batch, over the course of 20 days. The results from a representative lot are summarized in the table below:

Level	N	Mean (mg/L)	Within Run		Between Run		Total	
			SD	%CV	SD	%CV	SD	%CV
1	80	0.863	0.017	2.0%	0.010	1.2%	0.020	2.3%
2	80	1.647	0.009	0.5%	0.010	0.6%	0.016	1.0%
3	80	3.019	0.022	0.7%	0.014	0.4%	0.036	1.2%
4	80	5.063	0.024	0.5%	0.067	1.3%	0.078	1.5%
5	80	8.546	0.109	1.3%	0.000	0.0%	0.131	1.5%

b. *Linearity/assay reportable range:*

Linearity studies were performed following the recommendations in the CLSI EP06-A guideline. A high pool was prepared using a serum sample with high CRP activity. The low pool was pooled normal serum. The high and low pools were inter-diluted to achieve concentrations spanning 10% beyond the limits of the claimed measuring range (0.44 mg/L to 12.16 mg/L). The results were analyzed using weighted linear regression analysis and the results showed that the deviation from linearity did not exceed 10%.

The linearity studies support the claimed measuring range of 0.5 to 10 mg/L.

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

The assay is traceable to ERM-DA474, which is traceable to CRM 470.

d. *Detection limit:*

Detection limit studies were performed following the recommendations in the CLSI EP17-A2 guideline.

Limit of blank (LoB): The LoB was carried out using 4 depleted serum pools and 3 reagent lots using 1 instrument. Samples were run five times each per day, over 3 days to give a total of 60 replicates per reagent lot. For each reagent lot, the LoB results were ranked from lowest to highest concentration, and the LoB was estimated to be the result equivalent to the concentration at the 95th percentile.

Limit of detection (LoD): 4 serum sample pools were used to calculate the LoD using 3 reagent lots and 1 instrument. Samples were run five times each per day, over 3 days on each reagent lot. The LoD was calculated for each reagent lot using the parametric approach described in the guideline.

Limit of quantitation (LoQ): 4 serum sample pools were used to calculate the LoQ using 3 reagent lots and 1 instrument. Samples were run five times each per day, over 3 days on each reagent lot. The LoQ was determined using the lowest concentration that met the defined performance goals of imprecision (%CV) <20%.

Based on the results of the studies, the sponsor claims the following detection limits:

LoB	LoD	LoQ
0.15 mg/L	0.17 mg/L	0.5 mg/L

e. *Analytical specificity:*

Interference studies were performed following the recommendations in the CLSI EP07-A2 guideline. 4 pool levels of serum samples (with CRP concentrations around 1, 2, 3 and 5 mg/L) were used. Each sample was spiked with interfering substances and tested. Samples were tested in replicates of twenty at three analyte concentrations using a single lot of reagents. The results of the spiked samples were compared to the results of the non-spiked samples. At the following concentrations, the percentage difference between the results of the spiked samples compared to the results of the non-spiked samples was less that ±10%.

Potential Interferent	Highest Concentration Without Significant Interference
Hemoglobin	5 g/L
Intralipid	2000 mg/dL
Ibuprofen	2425 µmol/L
Triglyceride	1000 mg/dL
Warfarin	32.5 µmol/L
Acetaminophen	1324 µmol/L
Acetylsalicylic Acid	3.62 mmol/L
Conjugated Bilirubin	200 mg/L
Caffeine	308 µmol/L
Enalapril Maleate	0.86 µmol/L
Unconjugated Bilirubin	200 mg/L
Rheumatoid Factor	25 IU/mL

The sponsor includes the following information in the package insert.

"Turbidimetric assays are not suitable for measurement of highly lipaemic or haemolysed samples or samples containing high levels of circulating immune complexes (CICs) due to the unpredictable degree of non-specific scatter these sample types may generate. Unexpected results should be confirmed using an alternative assay method."

"Samples at selected CRP concentrations were spiked with decreasing concentrations of rheumatoid factor. The following results were obtained.

RF IU/mL	0.8mg/L CRP		1.5mg/L CRP		2.6mg/L CRP	
	mg/L difference	% difference	mg/L difference	% difference	mg/L difference	% difference
500	0.338	40.44%	0.394	26.70%	0.345	13.27%
250	0.484	62.50%	0.432	27.77%	0.37	13.79%
100	0.162	18.80%	0.197	12.02%	0.183	6.33%
50	0.145	17.40%	0.103	6.01%		
25	0.043	4.33%				

A sample at 3.8mg/L CRP showed <10% interference by 500 IU/mL RF. Any sample with an RF concentration greater than 25 IU/mL should be re-tested with an alternative method."

CRP prozone study:

A study was performed to verify the CRP prozone performance on the Optilite analyzer. 28 samples with CRP concentrations ranging from 0.8, to 1161.6 mg/L were evaluated. The study demonstrated that up to 829.3 mg/L the results were reported as above the measuring range and flagged as being out of the measuring range (>10 mg/L). However, due to antigen excess, samples with CRP concentrations above 893 mg/L will be reported erroneously low with a prozone flag. For example, a sample with a CRP concentration of 1161 mg/L is reported as 91.3 mg/L with a prozone flag.

The sponsor includes the following limitations in the labeling regarding the prozone effect:

"The reportable range of this assay is approximately 0.5 – 10mg/L, depending on lot-specific calibrator values. Any result obtained above this range must be considered invalid and the sample should be re-tested using a conventional CRP assay. For example, in a study samples between 893mg/L and 1161 mg/L returned falsely low concentrations (99.46 mg/L and 91.32 mg/L), however antigen excess was correctly detected by the analyser and results were accompanied by a "High activity" flag in all cases"

"Potential occurrences of antigen excess cannot be completely excluded. Samples detected as being in excess are flagged as "High activity" and are automatically re-measured at a higher sample dilution to confirm antigen excess. Any sample with a concentration above 10 mg/L should be considered invalid and re-tested with a conventional CRP assay."

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed using a total of 391 human serum samples. All samples were tested in singlicate using both the candidate and predicate device. 298 samples were within the measuring range of the candidate device. Data analysis was performed by Passing Bablok. The regression analysis is summarized in the table below

N	Slope	Intercept	95% CI Slope	95% CI Intercept
298	0.99	0.09	0.97-1.01	0.05-0.11

b. Matrix comparison:

Not applicable. The assay is only intended to be used with serum samples.

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):

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference interval:

The sponsor performed studies following the CLSI EP28-A3c guideline to verify the reference range of the analyte. A total of 50 serum samples were tested to verify the CRP reference interval. The verification studies support the following reference interval[1].

Consensus reference interval for adults: <3 mg/L

[1]Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-Reactive protein in healthy subjects; implications for reference intervals and epidemiological applications. Clin Chem 1997; 43: 52-8.

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.