510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K160070

B. Purpose for Submission:

Additional instrument clearance for a previously cleared device

C. Measurand:

Rheumatoid Factor

D. Type of Test:

Quantitative Immunoturbidimetric assay

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Rheumatoid Factor (RF) Kit for use on SPAPLUS®

G. Regulatory Information:

1. Regulation section:

   21 CFR § 866.5775, Rheumatoid factor immunological test system

2. Classification:

   Class II

3. Product code:

   DHR: System, test, Rheumatoid Factor

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use(s):

   The Rheumatoid Factor (RF) Kit for use on SPAPLUS® is intended for the quantitative in vitro measurement of rheumatoid factor in serum using the Binding Site SPAPLUS® analyser. Measurement of rheumatoid factor may aid in the diagnosis of rheumatoid arthritis. This test should be used in conjunction with other laboratory and clinical findings.

2. Indication(s) for use:

   Same as intended use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   SPAPLUS® turbidimetric analyser (K040958)

I. Device Description:

The Rheumatoid Factor Kit for use on SPAPLUS® contains:

Reaction Buffer: Containing glycine buffer (pH 8.3), sodium chloride, sodium ethylenediamine tetra acetric acid disodium salt dehydrate, bovine serum albumin, sodium azide (0.09%, w/v).

Latex Reagent: Containing glycine buffer (pH 7.3), sodium chloride, latex particle adsorbed human IgG, sodium azide (0.09%, w/v)

RF Controls: Supplied at two levels: Low and High. Target values and ranges are supplied in the Quality Control certificate. Supplied ready for use.

RF Calibrator 1–5: Calibration has been carried out and values have been assigned using an immunoturbidimetric method standardised to the international reference preparation, WHO Standard 64/2. Supplied ready for use.

J. Substantial Equivalence Information:

1. Predicate device name and 510(k) number:

   Roche Tina-Quant RF II assay on Modular P analyzer (K032535)

2. Comparison with predicate:

Similarities		
Item	**RF Kit on SPAPLUS®**	**Roche Tina-Quant RF II on Modular P**
Intended use	Turbidimetric *in vitro* quantification of rheumatoid factor	Same
Assay type	Quantitative	Same
RF Control	Two levels	Same
Calibration	WHO reference material NIBSC 64/2	Same

Differences		
Item	**RF Kit on SPAPLUS®**	**Roche Tina-Quant RF II on Modular P**
Specimen Type	Serum	Serum and plasma
RF Kit (reagent and buffer), Control and Calibrator packaging	RF Reagent, Buffer, Controls and Calibrators are packaged together as a kit	RF Kit (reagent and buffer), Controls and Calibrators are packaged individually and sold separately
Antibody	Human IgG anti-human-IgM	Human IgG
Calibrator	Five levels	Six Levels
Unopened Kit	12 months	Not stated
Open Vial Stability	Three months	90 days
On-board stability	30 days	90 days
Instrument	Binding Site SPAPLUS®	Roche Modular P
Measuring range	10–104 IU/mL (1/1: Standard Dilution) 70–1040 IU/mL (1/10: Automatic reflex dilution on high results at standard dilution)	7–130 IU/mL (1/1) Extended range up to 650 IU/mL
Expected value	<12.5 IU/mL	<14 IU/mL

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

- CLSI EP05-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 EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

- CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline

L. Test Principle:

The determination of soluble antigen concentration by turbidimetric methods involves the reaction with specific antiserum 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 from all studies met the manufacturer's pre-specified acceptance criteria.

a. Precision/Reproducibility:

The studies were based on CLSI EP05-A2. Five sample preparations were tested in two runs per day, each of the two runs in duplicate, over 21 days using three analysers and three lots of reagents. A summary of the results is shown below.

RF Sample	N	Mean IU/mL	Within-Run		Between-Run		Between-Day		Total Precision	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	84	13.8	0.37	2.7	0.44	3.2	1.16	8.4	1.29	9.3
2	84	19.6	0.28	1.4	0.69	3.5	1.12	5.7	1.34	6.9
3	84	39.4	0.34	0.9	0.17	0.4	1.83	4.6	1.87	4.7
4	84	72.4	0.82	1.1	0.00	0.0	5.77	8.0	5.83	8.0
5	84	173.3	3.11	1.8	3.76	2.2	15.52	9.0	16.27	9.4

RF Sample	N	Mean IU/mL	Between-lot		Between-instrument	
			SD	%CV	SD	%CV
1	84	13.8	1.17	8.5	0.22	1.6
2	84	19.6	1.08	5.5	0.40	2.0
3	84	39.4	1.35	3.4	0.38	1.0
4	84	72.4	6.10	8.4	0.00	0.0
5	84	173.3	14.57	8.4	9.81	5.7

b. Linearity/assay reportable range:

A linearity study was performed following CLSI guideline EP6-A. The linearity of this assay has been confirmed by diluton of serum samples with analyte-depleted serum to cover the range 10–104 IU/mL at a 1:1 sample dilution (total of 12 dilutions) and 70–1040 IU/mL at a 1:10 sample dilution (total of 13 dilutions). Deviation from linearity calculated according to CLSI guideline EP6-A was ≤ 9.9%. The regression equation for the high linear range (70–1040 IU/mL) was $y = 1.02x - 2.84$, and for the low linear range (10–104 IU/mL) was $y = 1.07x - 1.82$.

Antigen Excess:

No antigen excess was observed up to a level of approximately eight times the top of the calibration curve at the standard 1:1 sample dilution. This is equivalent to 8576.8 IU/mL at the 1:10 sample dilution.

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

(i) *Traceability*: The calibration of the assay is traceable to the WHO International Reference Preparation of Rheumatoid Arthritis Serum NIBSC 64/2.

(ii) Kit Stability:

Unopened kit stability: The manufacturer provided data that support a real-time stability claim of 12 months.

Open-vial stability: The RF Reagent, Calibrator and Controls can be stored opened at 2–8°C for up to three months.

On-board stability: The RF Reagent can be stored on-board the SPAPLUS® Analyzer for at least 30 days.

d. Detection limit:

The analytical sensitivity of both kits was determined in accordance with CLSI guideline EP17-A. The Limit of Blank (LoB) was based on 60 determinations of a blank sample (pool of analyte-depleted samples) and was estimated as the 95% percentile of the distribution. The Limit of Detection (LoD) was calculated according to the equation LoB + 1.645 x SDs where SDs, the standard deviation, was based on 12 determinations of 5 samples with analyte levels near the lower limit of the reportable range. The Limit of Quantitation (LoQ) was calculated from the total error of the LoD study. Total error at LoQ was within the maximum allowable total error for each sample matrix. The bottom of the measuring range, 10 IU/mL is set as the LoQ for this device.

Detection Limit Summary:

LoB = 0.475 IU/mL
LoD = 1.174 IU/mL
LoQ = 10 IU/mL

e. Analytical specificity:

Interferences were assessed according to CLSI EP07-A2 by testing samples at different RF concentrations. Each sample was spiked with interfering substances and tested and compared with results from non-spiked samples. The data demonstrated that the assay was not affected by the following substances at the concentrations given below.

Interferent	**Concentration**	**Interferent**	**Concentration**
Ascorbic Acid	342 µmol/L	Acetylsalicylic	1.815 mmol/L
Bilirubin, Conjugated	200 mg/L	Penicillin	75 mg/L
Hemoglobin	4 g/L	Caffeine	308 µmol/L
Intralipid	500 mg/dL	Prednisolone	100 µg/mL
Triglyceride	500 mg/dL	Digoxin	7.8 nmol/L
Acetaminophen	1324 µmol/L	Cimetidine	79.2 µmol/L
Ibuprofen	2425 µmol/L	Theophylline	222 µmol/L
Methotrexate	2 mmol	Phenytoin	198 µmol/L

f. Assay cut-off:

12.5 IU/mL

2. <u>Comparison studies:</u>

a. Method comparison with comparator device:

A comparison study was performed by analysing 324 samples (including 51 Rheumatoid Arthritis, 9 Osteoarthritis, 10 Psoriatic arthritis, 1 Juvenile Arthritis, 1 Spondyloarthritis, 17 SLE, 11 Sjögrens Syndrome, 2 Mixed Connective Tissue disease, 5 Lyme disease, 9 HCV, 5 Ulcerative Colitis, 5 Crohn's disease, 4 Celiac disease, 10 Syphylis, 5 Systemic Sclerosis, 4 Cirrhosis, 99 other clinical conditons, and 76 apparently healthy donor samples, covering the range 10.1–666 IU/mL) using the RF Kit on SPAPLUS® and a comparator assay. Passing Bablok regression analysis generated the following results:

y = 0.93x + 2.30 IU/mL (y = SPAPLUS®; x = comparator assay)

(95% CI: Intercept = 1.25 – 3.12; Slope = 0.90 – 0.97)

Correlation coefficient r = 0.98

The same comparison study was also analyzed with by calculating the % Positive Agreement, % Negative Agreement and % Overall Agreement calculations with the following results:

		Comparator Assay		
		Positive	Negative	Total
RF Kit on SPAplus	Positive	134	10*	144
	Negative	7**	173	180
	Total	141	183	324

* These ten samples had the following diseases/ conditions: four RA, one syphilis, one healthy donor and four other clinical conditions.
** These seven samples had the following diseases/ conditions: one RA, one osteoarthritis, one Sjögren's, one celiac, one ulcerative colitis, one Crohn's disease, and one donor.

Positive Percent Agreement: 95.0% (134/141) *(95% CI: 90.2% – 97.0%)*
Negative Percent Agreement: 95.0% (173/183) *(95% CI: 90.1% – 97.6%)*
Overall Percent Agreement: 95.0 % (307/324) *(95% CI: 91.8% – 96.7%)*

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity and specificity:

Not applicable.

b. Other clinical supportive data:

Not applicable

4. Clinical cut-off:

See assay cut-off above.

5. Expected value:

The values provided are intended for guidance purposes only. Expected values may vary with age, sex, sample type, diet and geographical location. Each laboratory should verify the transferability of the expected value to its own population and, if necessary, determine its own value.

The value was transferred from a comparator assay by ROC analysis with an AUC of 0.9.

Wherever possible it is strongly recommended that local values are generated.

	Expected value (IU/mL)
Rheumatoid factor	< 12.5

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.