510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k120750

B. Purpose for Submission:

New Device

C. Measurand:

Immunoglobulin M

D. Type of Test:

Turbidimetry, Quantitative

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Human IgM CSF Kit for use on SPA_{PLUS}

G. Regulatory Information:

1. Regulation section:

   21 CFR§866.5510 – Immunoglobulins A, G, M, D, and E immunological test system

2. Classification:

   Class II

3. Product code:

   CFN, Method, Nephelometric, Immunoglobulins (G, A, M)

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use(s):

   Human IgM CSF Kit for use on SPA_{PLUS} is intended for the quantitative measurement of human IgM in cerebrospinal fluid (CSF) samples using the SPA_{PLUS} analyzer. Measurement of this immunoglobulin aids in the assessment of the body's lack of ability to resist infectious disease in conjunction with other clinical and laboratory findings.

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   Prescription use only

4. Special instrument requirements:

   SPA_{PLUS} analyzer

I. Device Description:

The kit contains the following materials:

- Human IgM CSF Reagent SPA_{PLUS} (1 x 60 tests), Liquid
- Human IgM CSF SPA_{PLUS} Calibrator set 1-6 (6 x 1.0 mL), Lyophilized
- IgM CSF SPA_{PLUS} High Control (2 x 1.5 mL) and IgM Low Control (2 x 1.5 mL)
- IgM CSF Reaction Buffer SPA_{PLUS} (1 x 60 tests)

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(K) number(s):

   Siemens (Dade Behring) N Latex IgM (k032014)

2. Comparison with predicate:

Similarities		
Item	Device Human IgM CSF Kit for Use on SPA_{PLUS}	Predicate Siemens N Latex IgM
Intended use	For the quantitative measurement of human IgM in cerebrospinal fluid	*In vitro* diagnostic reagents for the quantitative determination of IgM in

Similarities		
Item	Device Human IgM CSF Kit for Use on SPA_{PLUS}	Predicate Siemens N Latex IgM
	(CSF) samples using the SPA_{PLUS} analyzer. Measurement of this immunoglobulin aids in the assessment of the body's lack of ability to resist infectious disease in conjunction with other clinical and laboratory findings.	human cerebrospinal fluid (CSF) and in paired CSF/serum samples by means of particle-enhanced immunonephelometry using the BN* Systems. The determination of IgM aids in the evaluation of the patient's immune system.
Analyte	Human IgM	Same
Sample type	CSF	Same
Reference range	<1.3 mg/L	Same

Differences		
Item	Device Human IgM CSF Kit for Use on SPA_{PLUS}	Predicate Siemens N Latex IgM
Method	Turbidimetry	Nephelometry
Instrument	SPA_{PLUS}	BNII system
Antibody	Sheep anti-human IgM	Rabbit anti-human IgM
Measuring range	0.3 – 7.0 mg/L (at 1/1 sample dilution) 3.0 – 70.0 mg/L (at 1/10 sample dilution)	0.13 – 4.2 mg/L
Stability	Open vial: 2 – 8°C for 2 months On-board: 30 days	Open vial: 2 – 8°C for 4 weeks On-board: N/A (should not be left open on a BNII system)

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

CLSI guideline EP05-A2 "Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition".
CLSI guideline EP06-A "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; 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 samples. Concentrations are automatically calculated by reference to a calibration curve stored within the instrument.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

For CSF samples, the precision was evaluated based on CLSI EP05-A2 by testing three pooled samples with low (0.524 mg/L), mid (1.258 mg/L), and high (6.291 mg/L) IgM concentrations. The study was done over 5 days with 2 runs per day; each sample was run in duplicate within each run. The results are summarized in the following table:

Sample	**Mean Conc.** (mg/L)	**Within-Run**		**Between-Run**		**Between-Day**		**Total**	
		SD (mg/L)	**CV** %	**SD** (mg/L)	**CV** %	**SD** (mg/L)	**CV** %	**SD** (mg/L)	**CV** %
Low	0.524	0014	2.7	0.012	2.3	0.014	2.7	0.023	4.4
Mid	1.258	0.008	0.7	0.015	1.2	0.014	1.1	0.022	1.7
High	6.291	0.031	0.5	0.096	1.5	0.086	1.4	0.133	2.1

To supplement the CSF precision data, three pooled sera samples with low, mid, and high IgG concentration were assayed in duplicate with 2 runs per day for 21 days (n=84) using three reagent lots and three instruments. Results are summarized below:

Mean Conc. (mg/L)	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
	SD (mg/L)	CV %	SD (mg/L)	CV %	SD (mg/L)	CV %	SD (mg/L)	CV %	SD (mg/L)	CV %
0.450	0.02	3.9	0.01	2.5	0.04	9.5	0.05	10.4	0.05	10.6
1.123	0.02	1.8	0.03	2.6	0.10	9.2	0.11	9.6	0.11	9.7
5.175	0.11	2.2	0.09	1.8	0.39	7.6	0.41	8.0	0.42	8.1

b. Linearity/assay reportable range:

Linearity: The linearity study was conducted based on CLSI EP06-A by analysis of a dilution series of pooled CSF sample. Each dilution was tested in triplicate. The observed values were graphed against the expected values and linear regression was performed. The results are summarized in the following table.

Sample range (mg/L)	Slope	Intercept	R^2	% Recovery
0.231 – 7.688	0.992	-0.103	0.999	86.6 – 100
0.221 – 7.378	0.994	-0.046	0.999	81.8 – 108
0.229 – 7.643	1.011	0.019	1.00	98.5 – 115.3

The claimed measuring range of the assay is 0.3 – 7.0 mg/L (at 1/1 sample dilution).

Antigen excess (hook effect): The susceptibility of the assay to antigen excess was investigated. The results demonstrated that the assay is not susceptible to antigen excess up to a concentration of 60 mg/L.

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

Traceability: The calibrators, the internal reference standards (IR) and controls are traceable to reference standard ERM-DA470k. IR is used to control calibration between batches.

The table below summarizes the target values for calibrators and controls:

	Target Value (mg/L)
Calibrator	
Calibrator 1	0.300
Calibrator 2	0.600
Calibrator 3	1.200
Calibrator 4	2.400
Calibrator 5	4.700
Calibrator 6	7.000
Controls	
High Control	4.00
Low Control	1.80

Stability:

Closed vial stability: The real time stability of IgM CSF kit was performed using three batches of kits stored under the recommended temperature at 2 – 8°C. Data were collected at point 0, 6.5, 10, 13 and 19 months. The results support stability of the kits under the recommended storage of 2 – 8 °C for 18 months.

Open vial stability: The study was done to evaluate the reagent stability after first opening. Three batches of kits were stored at 2 – 8°C after first opening. Data were collected at 1, 2, and 3 months. The results support that the reagents are stable once opened for 2 months when stored at 2 – 8°C.

On-board stability: On-board stability of IgM CSF was done by placing the kit in the

reagent carousel of the SPA_{PLUS}. The reagent carousel was covered and cooled to 8 – 12°C. A calibration curve was generated on Day 0 and validated with the IgM CSF kit controls. The test data were collected at Day 0, Day 14, and Day 35. The results support that the reagents are stables up to 30 days on-board the SPA_{PLUS}.

d. Detection limit:

The limit of blank (LoB) for this assay was determined by testing instrument diluent. The limit of detection (LoD) was determined by testing CFS sample with low IgM concentration. Sixty (60) replicates of each sample were run, and the mean and standard deviation for each of the samples was calculated. LoD = LoB + 1.645 x SDs where SDs is the standard deviation of the replicate samples. The LoQ was determined by testing the lowest calibrator fluid with assigned concentration at 0.293 mg/L. The results are summarized in the following table:

LoB	LoD	LoQ
0 mg/L	0.0322 mg/L	0.2463mg/L

e. Analytical specificity:

Endogenous interference: Interference by endogenous substances was evaluated by using one CSF sample base pool at the medical decision point (1.3 mg/L) spiked with hemoglobin and bilirubin. The negative samples were prepared by spiking the same volume of commercially obtained blanks reagents into the CSF pool. The resulting samples were tested in triplicate and the mean values were used to calculate % interference. No significant interference was noted for sample containing hemoglobin at 2.5 g/L and bilirubin at 100 mg/L.

Drug interference: Interference by drugs was evaluated by using one CSF sample base pool (at concentration of 1.3 mg/L) spiked with acetaminophen and aspirin dissolved in distilled water. The negative samples were prepared by spiking the CSF pool with the same volume of distilled water. All samples were tested in triplicate and the mean values were used to calculate % interference. No significant interference was observed for sample containing acetaminophen at 200 mg/L and aspirin at 600 mg/L.

Bacterial interference: No bacterial interference study was performed. In the labeling, the following statement is added in section of Limitations of the package insert:
"*Bacterial interference has not been assessed. CSF samples should be as fresh as possible to limit bacterial growth and all samples must be centrifuged prior to testing (see section 7)*".

f. Assay cut-off:

The cut-off is the same as the predicate and is defined as the upper limit of the

reference range (established from literature). The reference range for IgM in CSF is <1.3 mg/L.

2. Comparison studies:

   a. Method comparison with predicate device:

   A method comparison study was performed to compare the IgM CSF kit on SPA_{PLUS} (y) and the predicate device on BNII system (x) using CSF samples. Total 58 samples including 32 normal and 26 clinical CSF samples were tested. Samples covered the measuring range for both proposed and predicate devices. The comparison analysis showed the following equation (Passing/Bablok):

N=	Sample range (mg/L)	Comparison (Passing/Bablok)
58	0.32 – 4.05	y =1.08x – 0.02 Slope (95% CI): 1.00 – 1.15 Intercept (95% CI): -0.07 – 0.04

   b. Matrix comparison:

   Not applicable, assay use CSF sample only

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:

   See assay cut-off

5. Expected values/Reference range:

   The reference range for IgM in CSF is <1.3 mg/L according to the literature. It is strongly recommended that each facility should determine its own reference intervals. The reference values in the true sense only exist to the CSF/serum ratio.

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.