

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

A. 510(k) Number:

k120749

B. Purpose for Submission:

New Device

C. Measurand:

Immunoglobulin G

D. Type of Test:

Turbidimetry, Quantitative

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Human IgG 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 IgG CSF Kit for use on SPA_{PLUS} is intended for the quantitative measurement of human IgG 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 IgG CSF Antiserum SPA_{PLUS} (1 x 60 tests), Liquid
- Human IgG CSF SPA_{PLUS} Calibrator set 1-6 (6 x 1.0 mL), Lyophilized
- CSF SPA_{PLUS} High Control (2 x 1.5 mL) and Low Control (2 x 1.5 mL)
- Reaction Buffer (1 x 60 tests)

J. Substantial Equivalence Information:

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

N Antisera to Human Immunoglobulin (IgG, IgA and IgM) (k083445)

2. Comparison with predicate:

Similarities and Differences		
Item	Device Human IgG CSF Kit for Use on SPA _{PLUS}	Predicate N Antisera to Human Immunoglobulin (IgG, IgA and IgM)
Intended use	For the quantitative measurement of human IgG in cerebrospinal fluid (CSF) samples using the	For the quantitative measurement of immunoglobulins (IgG, IgA, and IgM) in human serum,

Similarities and Differences		
Item	Device Human IgG CSF Kit for Use on SPA _{PLUS}	Predicate N Antisera to Human Immunoglobulin (IgG, IgA and IgM)
	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.	heparinized and EDTA plasma, and IgG in human urine and cerebrospinal fluid (CSF) by means of nephelometry on the BN TM Systems. Measurements of these immunoglobulins aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents
Analyte	Human IgG	Human IgG, IgA, and IgM
Sample type	CSF	Serum, heparinized and EDTA plasma, human urine and CSF
Method	Turbidimetry	Nephelometry
Instrument	SPA _{PLUS}	BN system
Antibody	Sheep anti-human IgG	Rabbit anti-human IgG, IgA, IgM
Measuring range	4.2 – 135 mg/L (at 1/1 sample dilution) 42 – 1350 mg/L (at 1/10 sample dilution)	3.6 – 115 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: 5 days with 8 hours/day
Reference range	<34 mg/L	Same

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 (7.45 mg/L), mid (31.71 mg/L), and high (125.53 mg/L) IgG concentrations. The study was done over 5 days with 2 runs per day; each sample was run in duplicate within each run on one lot of reagent on one instrument due to the limited availability of CSF samples. 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	7.45	0.12	1.6	0.41	5.5	0.25	3.3	0.49	6.6
Mid	31.71	0.27	0.9	1.58	5.0	2.04	6.4	2.59	8.2
High	125.53	1.26	1.0	6.19	4.9	0	0	6.31	5.0

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:

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	6.00	0.21	3.5	0.65	7.8	0.26	4.3	0.73	8.3
Mid	31.82	0.57	1.7	2.61	7.7	0	0	2.67	7.9
High	101.54	2.24	2.0	1.60	1.4	2.27	2.0	3.56	3.2

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
5.95 – 129.17	0.997	-2.507	0.999	87.5 – 100.0
6.78 – 135.65	1.000	-0.489	0.998	93.4 – 102.3
11.08 – 110.80	1.037	-2.303	0.999	88.1 – 103.3
4.11 – 54.75	0.998	-0.693	1.000	85.6 – 100.0

The claimed measuring range of the assay is 4.2 – 135 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 700 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	4.2
Calibrator 2	8.4
Calibrator 3	16.8
Calibrator 4	33.8
Calibrator 5	67.5
Calibrator 6	135
Controls	
High Control	85
Low Control	30

Stability:

Closed vial stability: The real time stability of IgG CSF kit was performed using three batches of kits stored under the recommended temperature at 2 – 8°C. Data were collected at point 0, 3, 7, 10, 13, 19, and 25 months. The results support stability of the kits under the recommended storage of 2 – 8°C for 24 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 up to 2 months when stored at 2 – 8°C.

On-board stability: On-board stability of IgG 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 IgG CSF kit controls. The test data were collected at Day 0, Day 14, and Day 35. The result supports that the reagents are stable 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 IgG concentration. Sixty (60) replicates of each sample were run, and the mean and standard deviation for each of the samples was calculated. $LoD = LoB + 1.645 \times SDs$ where SDs is the standard deviation of the replicate samples. The LoQ was tested using the lowest calibrator fluid with assigned concentration 3.802 mg/L. The claimed LoB, LoD and LoQ are summarized in the following table:

LoB	LoD	LoQ
0 mg/L	0.6925 mg/L	4.4601 mg/L

e. *Analytical specificity:*

Endogenous interference: Interference by endogenous substances was evaluated by using one CSF sample base pool at the medical decision point (34 mg/L) spiked with hemoglobin and bilirubin. The negative samples were prepared by spiking the same volume of commercially obtained blank 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 34 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 IgG in CSF is <34 mg/L.

2. Comparison studies:

a. *Method comparison with predicate device:*

A method comparison study was performed to compare the IgG CSF kit on SPA_{PLUS} (y) and the predicate device on Siemens BNII system (x) using CSF samples. Total 96 samples including normal and clinical CSF samples were tested. 27 out of 96 samples were spiked with IgG in order to fully span the measuring range for both proposed and predicate devices. The results were summarized as follows:

N=	Sample range (mg/L)	Comparison (Passing/Bablok)
96	4.39 – 114.00	$y = 1.05x - 0.27$ Slope (95% CI): 1.02 – 1.08 Intercept (95% CI): -1.51 – 0.90

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 IgG in CSF is <34 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.