

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

A. 510(k) Number:

k120901

B. Purpose for Submission:

New Device

C. Measurand:

IgA antibody

D. Type of Test:

Quantitative, turbimetric

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Human IgA CSF Kit for use on the 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 IgA CSF kit for use on SPA_{PLUS} is intended for the quantitative measurement of human IgA in cerebrospinal fluid (CSF) samples using the SPA_{PLUS} analyser. 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:

Materials provided:

- 1X60 Tests Human IgA CSF Antiserum Reagent SPA_{PLUS}, Liquid
- Calibrator set – Human IgA CSF, 6 vials (1-6), lyophilized
- 2x1.5 mL IgA CSF high control
- 2x1.5 mL IgA CSF low control
- 1x60 tests IgA CSF reaction buffer

Materials required but not provided:

- Equipment for collection and preparation of test samples e.g. sample tubes, centrifuge, etc.
- A fully operational and equipped SPA_{PLUS} analyzer
- Current analyzer operating instructions: SPA_{PLUS} Reference Guide, Insert Code FINO12
- Sample diluent (used as 1/100) Product Code SN080.S
- 2% alkaline wash solution (working dilution)
- Distilled water

J. Substantial Equivalence Information:

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

N Latex IgA (k024038)

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	Human IgA CSF Kit for Use on SPA _{PLUS}	N Latex IgA
Intended use	This assay is intended for the quantitative measurement of human IgA 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.	Same

Differences		
Item	Device	Predicate
	Human IgA CSF Kit for Use on SPA _{PLUS}	N Latex IgA
IgA Reagent	Monospecific sheep antibody coated onto polysterene latex and is supplied in liquid form	Freeze-dried polystyrene particles coated with Rabbit anti-human IgA
Detection	Turbidimetry	Nephelometry
Instrument	SPA _{Plus} analyser	BNII system
Antibody	Sheep antiserum to human IgA	Rabbit antiserum to human IgA
Sample matrix	CSF	CSF and serum
Measuring range mg/L	0.15 – 4.8 (1/1) 1.5 – 48.0 mg/L (1/10)	1.25 – 41.8 mg/L (1/5)
Open vial stability	2 months	4 weeks
On board stability	30 days	3 days at 8 hours each day

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

CLSI EP5-A Evaluation of Precision Performance of Quantitative Methods;
Approved Guideline – Second Edition
CLSI EP6-A Evaluation of Linearity of Quantitative Measurement Procedures;
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 (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The study was carried out using three serum pools; 1 low (2.545 mg/L), 1 mid (5.439 mg/L) and 1 high (34.085 mg/L) analyte concentration. Analysis was carried out over 21 days with 2 runs (each of the two runs in duplicate) per day (N=84), using three reagent lots and four instruments. The results for samples are summarized in the table below:

Mean mg/L	Within-Run		Between-Run		Between-Day		Total	
	SD	CV%	SD	CV%	SD	CV%	SD	CV%
34.085	0.486	1.4	0.227	0.7	1.896	5.6	1.971	5.8
5.439	0.122	2.2	0.057	1.1	0.399	7.3	0.422	7.8
2.546	0.080	3.1	0.041.6	1.6	0.193	7.6	0.213	8.4

A study to compare precision between 3 lots was done using the serum samples. The %CV between lots was <10%.

Three additional samples in CSF (pooled), 1 low (1.986 mg/L), 1 mid (5.290 mg/L) and 1 high (46.164 mg/L) analyte concentration, were also tested over 5 days with 2 runs (each of the two runs in duplicate) per day (N=20), using one reagent lot and one instrument. The results are summarized in the table below:

Mean mg/L	Within-Run		Between-Run		Between-Day		Total	
	SD	CV%	SD	CV%	SD	CV%	SD	CV%
46.164	0.185	0.4	0.499	1.1	0.630	1.4	0.825	1.8
5.290	0.062	1.2	0.041	0.8	0.350	6.6	0.358	6.8
1.986	0.099	5.0	0.118	5.9	0.000	0.0	0.154	7.8

b. *Linearity/assay reportable range:*

Linearity:

The linearity was established by analysis of dilution series of pooled CSF spiked with pure protein (49.46 mg/L, 6.06 mg/L, 22.358 mg/L and 25.733 mg/L). The latter two samples were prepared by using CSF low pool samples as diluent. Results were evaluated at each concentration against pre-defined goals for recovery and %CV:

Concentration range (mg/L)	slope	Intercept	r ²	% recovery
49.46 – 1.35	0.993	0.7159	0.999	100.0 - 117.7
6.06 – 0.118	0.9927	0.1223	0.9963	83.6 – 101.6
22.358 – 0.938	0.994	-0.159	0.9996	90.3 – 100.0
25.733 – 0.867	1.003	-0.119	0.9998	91.4 – 101.4

The claimed measuring range of the assay is:

0.15 - 4.5 mg/L (at 1/1 sample dilution) for very low CSF IgA concentration
1.50 – 48.0 mg/L (at 1/10 sample dilution)

Over the range detection:

It has been demonstrated that the assay does not give results in antigen excess up to a concentration of 228.3 mg/L at 1/10 dilution. Samples giving results below the lower limit of the measuring range at standard sample dilution (1/10) are auto-rediluted to 1/1. Results which are still outside of the measuring range following auto re-dilution of 1/1 are reported as <0.15mg/L. Results above the measuring range at 1/10 are reported as > 48 mg/L.

High dose hook effect:

Over the range assay study was done and showed no antigen excess up to a concentration of 22.83 mg/L at neat instrument dilution. This is equivalent to 228.3 mg/L at instrument dilution 1/10. The claim is 90 mg/L at 1/10 dilution.

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. The IR is prepared from pooled human sera and is used to control calibration between lots. The table below summarizes the calibrators and controls target values:

	Target Value (mg/L)
Calibrator	
Calibrator 1	0.15 mg/L
Calibrator 2	0.30 mg/L
Calibrator 3	0.60 mg/L
Calibrator 4	1.20 mg/L
Calibrator 5	2.40 mg/L
Calibrator 6	4.80 mg/L
Controls	
High control	25.0 mg/L
Low control	4.5 mg/L

Stability:

Calibrators are supplied lyophilized; Controls are supplied in liquid form. Real-time stability study is ongoing. The stability claims are summarized below:

Stability Claims	
After opening	
Kit (IgA reagent, reaction buffer, calibrators (post reconstitution) and controls)	2 months at 2-8°C, capped)
On board	
IgA reagent, reaction buffer	30 days, uncapped (the reagent carousel is covered and cooled to 8-12°C)
Shelf life	
Real time kit stability	6.5 months at 2-8°C

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 a CSF sample with low IgA concentration; $LoD = LoB + 1.645 \times SD$ where SD is the standard deviation of the replicate samples. The LoQ sample was a calibrator fluid with assigned concentration 0.162 mg/L. Sixty (60) replicates of each sample were run; the mean and SD for each of the samples was calculated. The results are summarized below:

LoB	LoD	LoQ
0 mg/L	0.0232 mg/L	0.237 mg/L

e. Analytical specificity:

Interference by endogenous substances:

Interference by endogenous substances were evaluated by addition of

hemoglobin (2.5 g/L), bilirubin (100 mg/L) test serum samples representing analyte concentrations at the medical decision point (sample 5 mg/L). No significant interference was observed with the interferents tested. Rheumatoid factor was not evaluated.

Drug interference:

Interference by drugs was evaluated by using one CSF sample base pool (at concentration of 5 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. The following statement is added in the Limitations section 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*”.

f. *Assay cut-off:*

This cut-off is the same as the predicate and is defined as the upper limit of the reference range, which was obtained from literature and is <5 mg/L. The cut-off was validated.

2. Comparison studies:

a. *Method comparison with predicate device:*

Thirty-seven (37) clinical CSF samples and 56 normal CSF samples were used in the study. Samples were obtained from subjects with suspected medical condition. Samples giving results outside of the measuring range could not be included in the study. The samples for the comparison study ranged 0.49 – 41.1 mg/L. Regression analysis (Passing Bablok) of these samples is summarized below:

Regression equation	n	95% CI of Slope	95% CI of Intercept	R ²
$Y = 0.960x - 0.05g/L$	93	0.92 – 0.99	-0.24 – 0.04	0.94

b. *Matrix comparison:*

Not applicable, assay in CSF 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 literature reference range for IgA in CSF is <5mg/L. 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.