510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k103824

B. Purpose for Submission:

Modification to cleared device (k081827)

C. Measurand:

IgA Antibody

D. Type of Test:

Quantitative, turbidimetric

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Human IgA Liquid Reagent Kit for use on SPA_{PLUS}™

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.5510 – Immunoglobulins A, G, M, D, E Immunological Test System

2. Classification:

   Class II

3. Product codes:

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

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use(s):

   This kit is intended for the quantitative *in vitro* determination of human IgA in serum, lithium heparin or EDTA plasma, using the Binding Site SPA_{PLUS}™ turbidimetric analyser. Measurement of IgA aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents. The test results are to be used in conjunction with other clinical and laboratory 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:

   The Binding Site SPA_{plus}™

I. Device Description:

The device consists of the following: monospecific sheep anti-IgA antisera in liquid form in the presence of preservatives. Calibrators 1-6; Normal and High controls in liquid form; and IgA reaction buffer. The reagents contain 0.099% sodium azide, 0.1% EACA and 0.01% benzamidine as preservatives.

J. Substantial Equivalence Information:

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

   Roche Tina-quant IgA Gen.2/ Hitachi, k040435

2. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative determination of IgA in serum or plasma	Same
Detection Method	Turbidimetric immunoassay	Same
Controls	Normal and High levels, liquid, ready-to-use	Same

Differences		
Item	Device	Predicate
Sample Matrix	Human serum; lithium heparin or EDTA plasma	Human serum; lithium/ sodium heparin or EDTA plasma
Antibodies	Sheep	Goat
Instruments	SPA_{PLUS}™ turbidimetric analyser	Roche/ Hitachi automated clinical analyser
Traceability	Standardized against ERM-DA470k European Reference Material (previously CRM470)	Standardized against CRM 470 International Reference Material
Measuring range	0.2 – 7.0 g/L Extended range with rerun: 0.02 – 28.0 g/L	Hitachi: 0.5 – 8.0 g/L Extended range with rerun: 0.05 – 45.0 g/L
Reference Ranges	Adults: 0.845 – 4.99 g/L Pediatric: 0.00 – 3.58 g/L (refer to specific ranges/ age in 'Expected values/ Reference Range' Section below Referenced to Lockitch et al Clin Chem 1988)	Adults: 0.7 – 4.0 g/L Pediatric: 0.00 – 3.58 g/L (same as in new device)

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

CLSI EP-5A2: Evaluation of Precision Performance of Clinical Chemistry; Approved Guideline – Second Edition

CLSI EP-6A: Evaluation of Linearity of Quantitative Measurements; Approved Guideline

CLSI EP-17A: Determinations of Limits of Detection and Limits of Quantitation; 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 photoiodide 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 within the instrument. Addition of a low level range at a neat sample dilution (0.02 – 0.7 g/L) to the device previously cleared in k081827 allows samples to be measured blow 0.2 g/L. The sample volume has changed from 25 µL to 8 µL to allow samples to be run at neat.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The intra-assay and inter-assay precision was determined by testing four serum samples over 21 days with two runs per day on three different reagent lots on three analysers. Results are summarized below.

Sample	Mean (g/L)	Within-Run		Between-Run		Between-Day		Total	
		SD	CV %	SD	CV %	SD	CV %	SD	CV %
Serum 1	5.895	0.06	1.0	0.08	1.4	0.18	3.1	0.21	3.5
Serum 2	3.606	0.025	0.7	0.06	1.7	0.11	3.1	0.13	3.6
Serum 3	0.340	0.003	0.9	0.01	1.0	0.02	4.9	0.02	5.1
Serum 4	0.073	0.001	2.0	0.0004	0.5	0.003	3.8	0.003	4.3

b. Linearity/assay reportable range:

Linearity across the assay range (0.02 – 28.0 g/L) was confirmed by testing two serum pools with high range concentrations up to 30.9 g/L and one serum pool with low concentrations from 0.5 – 7.6 g/L. The samples were serially diluted 9 times with buffer (1:10) down to the lower measuring range (0.02 g/L). All testing were performed twice. The regression plot equations where y is the measured level of IgA concentration and x the theoretical concentration were as follows:

Serum Pool	Concentration Range (g/L)	Slope	Intercept	r^2
1	0.02 – 0.60	0.9664	0.004	0.9981
2	0.32 – 7.64	0.9874	0.074	0.9997
3	2.49 – 30.9	1.007	0.209	0.9993

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

An internal reference standard (IR7990) was assigned by comparison with the European Reference Material ERM-DA470k (previously CRM470 International Reference Material).

Stability: Stability studies demonstrated that the unopened and opened kits were stable at 2 – 8°C for 6 months and 3 months, respectively, and that on-board IgA kit are stable for 30 days.

d. *Detection limit:*

The detection limits were determined by testing 60 replicates of a blank sample, the lowest calibrator, or a sample with value close to the blank sample. The limit of blank claim for this assay is 0.001 g/L as determined by testing 60 replicates of a blank sample. The limit of detection represents the lowest measurable analyte level that can be distinguished from zero and has been estimated at 0.003 g/L. The limit of quantitation is defined as the lowest amount of analyte that can be quantitatively determined and has been estimated as 0.020 g/L for this assay.

e. *Analytical specificity:*

Interference by endogenous and other substances:

No significant assay interference by 1500 formazine turbidity units (FTU) of chyle, 200 mg/L bilirubin, or 5g/L hemoglobin using IgA sample at 0.255 g/L. No interference is demonstrated with rheumatoid factor (RF 546 IU/mL).

There is no cross reactivity between IgA and IgG or IgM under normal assay conditions.

The package insert states that “turbidimetric assays are not suitable for measurement of highly lipemic or hemolyzed samples, or samples containing high levels of circulating immune complexes due to the unpredictable degree of non-specific scatter these sample types might generate. Unexpected results should be confirmed using alternative assay method”.

Antigen excess effect:

The possibility of antigen excess occurring when using the device on The Binding Site SPA_{PLUS}™ was evaluated with 2 serum samples with IgA concentrations above the assay range (53.00 and 47.10 g/L). No antigen excess effect up to 40.10 g/L of IgA was observed.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study between Human IgA Liquid Reagent Kit on a SPA_{PLUS}™ analyzer and predicate device was performed using 262 samples (88 normal, 152 known elevated or suppressed IgA samples and 22 low level samples diluted to obtain results between 0.020 and 0.070g/L). A total of 55 samples were excluded: 39 samples with results of <0.04 g/L which is the LoQ of the predicate device and 16 samples with results of >25.12 g/L which is the upper limit of the new device. The study demonstrated the following Passing-Bablok fit: y = 1.00x + 0.000 (g/L) with a correlation coefficient (r) of 0.995.

Per ESID (European Society for Immunodeficiency) IgA Guidance Document, a result of less than 0.070 g/L was considered to be positive (i.e. an IgA deficient subject) and a result of greater than or equal to 0.070 g/L was considered to be negative. Percent agreements between IgA Liquid Reagent Kit on a SPA_{PLUS}™ analyzer and predicate in identifying IgA deficient samples were calculated as summarized in the table.

		Predicate device IgA kit		
		positive	negative	Total
New device IgA Kit	positive	59	3	62
	negative	3	197	200
	Total	62	200	262

Positive percent agreement: 95.16% (95% CI: 0.867 – 0.983%)

Negative percent agreement: 98.5% (95% CI: 0.957 – 0.995%)

Overall percent agreement: 97.71% (95% CI: 0.936 – 0.986%)

An additional correlation study was performed using 58 normal and 41 clinical samples from a pediatric population (<2 months to <21 years). Results from Passing-Bablok regression show linear fit: y = 1.03x - 0.01; r = 0.996.

b. *Matrix comparison:*

Serum versus plasma correlation were tested on 30 matched normal serum plasma samples over the range of 1.0 to 6.3 g/L. Comparison was also performed on 25 µL and 8 µL volumes on Serum versus lithium heparin plasma and Serum versus EDTA plasma studies. Results from linear regressions analyses are summarized in the table below.

Comparison	N	IgA Liquid Reagent Kit	95% CI	R^2
Serum vs Lithium Heparin	30	y =0.9747x - 0.006	0.94 – 1.01%	0.993
Serum vs EDTA	30	y = 0.9775x + 0.0318	0.95 – 1.00%	0.993

3. Clinical studies:

a. Clinical Sensitivity and specificity:

A clinical study evaluated 33 samples on this kit : 17 IgA deficient samples (11 of which were pediatric: 3 – 17 yrs), 7 non-target disease samples (1 chronic lymphocytic leukemia, 1 lambda light chain paraprotein, 1 primary biliary cirrhosis, 1 myeloma and 3 Waldenström's Macroglobulinemia) and 9 samples from normal individuals. The 17 IgA deficient clinical samples all had IgA levels below 0.07 g/L and the 16 remaining samples had levels above 0.07 g/L. These results support the claim that this kit is able to identify IgA deficiency according to the ESID Guideline.

b. Other clinical supportive data (when a. is not applicable):

Not applicable.

4. Clinical cut-off**:**

Not provided.

5. Expected values/Reference range:

Adult reference range:

Adult reference range was assessed using a total of 258 serum samples from healthy adult blood donors at 2 sites. A non-parametric distribution of IgA results was seen that gave a 95 percentile reference interval of 0.850 – 4.990 g/L with a mean of 0.2464 g/L and a median of 2.297 g/L.

Pediatric reference range:

Pediatric expected ranges per Lockitch et al (Clin Chem 34/8, 1988) have been included in the Package insert as follows:

Age Group (years)	Number (n)	95 Percentile Range (g/L)
Less than 1	75	0.00 – 0.83
1 – 3	52	0.20 – 1.00
4 – 6	41	0.27 – 1.95
7 – 9	55	0.34 – 3.05
10 – 11	38	0.53 – 2.04
12 – 13	38	0.58 – 3.58
14 – 15	38	0.47 – 2.49
16 – 19	74	0.61 – 3.48

Normal ranges for pediatric subgroups were assessed with data from 58 healthy children and juveniles. The pediatric ranges were as follows:

Pediatric subgroups	Age (years)	n	Concentration ranges (g/L)
Infant	< 2	6	0.02 – 2.58
Child	2 – <12	34	0.26 – 2.56
Adolescent	12 – <18	18	0.48 – 3.01
Transitional Adolescent A/B	18 – < 21	14	0.60 – 3.84

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.