

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

**A. 510(k) Number:**

k082129

**B. Purpose for Submission:**

New device

**C. Measurand:**

Immunoglobulin M (IgM)

**D. Type of Test:**

Quantitative immunoturbidimetric assay

**E. Applicant:**

The Binding Site Ltd.

**F. Proprietary and Established Names:**

Human IgM 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

21 CFR § 862.1150, Calibrator

21 CFR § 862.1660, Quality Control Material (Assayed and Unassayed)

2. Classification:

Class II, Device and Calibrator

Class I, Quality Control Material

3. Product code:

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

JIT, Calibrator, Secondary

JJX, Single (specified) analyte controls (assayed and unassayed)

4. Panel:

Immunology (82)

Chemistry (75)

**H. Intended Use:**

1. Intended use(s):

This kit is intended for the quantitative *in vitro* determination of human IgM in human serum, heparinized or EDTA plasma, using the Binding Site SPA<sub>PLUS</sub><sup>TM</sup> turbidimetric analyser. Measurement of IgM 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:

For use on the SpaPlus analyzer.

**I. Device Description:**

The device consists of: reaction buffer, sheep anti-IgM antiserum, six calibrators and two controls. The calibrators and controls are based on stabilized human serum. All components contain sodium azide as a preservative and are provided in ready-to-use liquid format.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):  
Roche Tina-quant IgM Gen 2
2. Predicate K number(s):  
k040431
3. Comparison with predicate:

<b>Similarities</b>		
Item	Device	Predicate
Intended Use	This kit is intended for the quantitative <i>in vitro</i> determination of human IgM in human serum, heparinised or EDTA plasma, using the Binding Site SPA <sub>PLUS</sub> <sup>TM</sup> turbidimetric analyser. Measurement of IgM 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.	Same
Sample Type	Human serum, heparin and EDTA plasma	Same
Methodology	Turbidimetric immunoassay	Same
Traceability	CRM 470	Same
Control and Calibrator Format	liquid ready-to-use	Same

<b>Differences</b>		
Item	Device	Predicate
Antibody	Sheep	Goat
Instrument	SpaPlus analyzer	Roche/ Hitachi automated clinical chemistry analyzers
Calibrators	Included in kit	Available separately
Controls	Included in kit	Available separately

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

CLSI EP5-A: Approved Guideline for Evaluation of Precision Performance of

Clinical Devices

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

**L. Test Principle:**

Human IgM in the sample reacts specifically with anti-human IgM antibodies to yield insoluble aggregates. When light is passed through the suspension 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:*

Reproducibility testing followed CLSI EP5-A. Three serum samples (low, medium, and high) were assayed in duplicate for 2 runs per day for 21 days (n=84) on SpaPlus analyzers. Results are shown in the table below:

	Mean (g/L)	Within Run		Total	
		SD	%CV	SD	%CV
Serum 1	0.36	0.001	2.3	0.02	6.2
Serum 2	2.79	0.02	0.6	0.11	3.9
Serum 3	6.44	0.04	0.6	0.14	2.1

Dilution Study:

To validate the accuracy and precision of automated sample dilution protocol Serum 2 and 3 (above) were automatically diluted by the instrument to 1/40 and tested on a single run 20 times; the mean (95% CI) and percent difference from the standard 1:20 dilution (above) were calculated:

	Mid-level	High Level
Mean	2.8369g/L	6.5604g/L
SD	0.032	0.056
%CV	1.1%	0.9%
1:20 mean	2.7884g/L	6.4445g/L
% difference	+1.7%	+1.8%

b. *Linearity/assay reportable range:*

The measuring range for the assay is 0.2 – 7.5 g/L. The procedure used to determine linearity was based on CLSI EP6-A. Three samples containing a high level of IgM and one sample containing a moderate level of IgM were serially diluted to cover the claimed assay range. Each dilution was assayed in duplicate and plotted versus the relative analyte concentrations (% dilution).

Results from each sample were evaluated by regression analysis and demonstrated linearity over the claimed range. The regression equation was:  $y = 0.996x - 0.0004 \text{ g/L}$  ( $R^2=0.98$ )

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

The calibrator is traceable to the International Reference Preparation CRM470. The controls are assigned on calibration curves validated with an internal reference standard directly assigned to the international reference standard CRM470. The controls supplied with each lot are assayed on the kit and information on the values obtained, including the +/-15% customer range, are found in the lot specific quality control certificate.

Opened IgM Antiserum and Reaction Buffer were shown to be stable for up to 30 days on board the SPAplus analyzer. Unopened (capped) reagents, calibrators and controls were shown to be stable for at least 90 days when stored at 2 – 8°C.

d. *Detection limit:*

Limit of the blank (LoB) and limit of detection determination followed CLSI EP17-A. LoB was calculated by taking the mean absorbance of 60 replicates of the blank plus 2 standard deviations. This was equivalent to 0.001 mg/dL. LoD was determined by taking the mean absorbance of a sample known to have a very low level of IgM. This was equivalent to 0.004 mg/dL. The sponsor claims the limit of quantitation (LoQ) as the lowest calibrator which has a value of 0.2 mg/dL.

e. *Analytical specificity:*

Bilirubin, hemoglobin, Rheumatoid Factor, and chyle, showed no significant interference at 200mg/L, 4.82g/L, 600 IU/mL, and 2820 formazine turbidity units (FTU's) respectively.

f. *Assay cut-off:*

Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

A study correlating the results of the human IgM Kit on the SPAplus analyzer and a commercially available IgM assay was performed using 71 samples (42 normal serum, 26 clinical serum, and 3 clinical plasma samples). Samples ranged from 0.28 to 6.20 g/L (by the predicate method). Passing-Bablok regression analysis of these samples yielded the following:  $y = 1.01x - 0.02 \text{ g/L}$ . The correlation coefficient ( $R^2$ ) calculated from a linear regression analysis was 0.994.

b. *Matrix comparison:*

The suitability of EDTA plasma and lithium heparin plasma was evaluated by comparing their IgM concentrations to matched serum samples. from 35 subjects (27 normal subjects, six Waldenstrom macroglobulinemia patients and two IgA myeloma patients). Samples were stored at -20°C before assaying.

Thirty-three matched serum and lithium heparin plasma samples between 0.3 to 6.7g/L yielded a relationship of  $y = 0.974x + 0.03$   $r = 0.998$  ( $R^2=0.997$ ). Percentage difference from the serum sample ranged from -4.4% to 11.7%

with a mean difference of -0.1%.

Twenty-four matched serum and EDTA plasma samples between 0.4 to 3.1g/L yielded a relationship of  $y=0.956x + 0.043$   $r=0.999$  ( $R^2=0.997$ ).

Percentage difference from the serum sample ranged from -6.7% to 16.2% with a mean difference of 0.3%.

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:

Not applicable.

5. Expected values/Reference range:

120 normal serum samples were obtained from healthy adult blood donors (17 – 70 years of age). Samples were stored at -20 C before testing. A non-parametric distribution of IgM results was seen. The mean was 1.02 g/L with a median value of 0.85 g/L; the 95<sup>th</sup> percentile range was 0.35 – 2.42 g/L.

During childhood and adolescence, reference ranges for IgM are dependent on age and can vary over a wide range. Each laboratory should establish its own expected values for IgM since values may differ depending on the population studied.

**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.