

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE**

A. 510(k) Number:

k141100

B. Purpose for Submission:

New device

C. Measurand:

Complement C1 inactivator (inhibitor)

D. Type of Test:

Quantitative immunoturbidimetry

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Optilite® C1 Inactivator Kit

G. Regulatory Information:

1. Regulation section:
21 CFR 866.5250 Complement C1 inhibitor (inactivator) immunological test system
2. Classification:
Class II
3. Product code:
DBA, Complement C1 inhibitor (inactivator) antigen, antiserum, control
4. Panel:
Immunology (82)

H. Intended Use:

1. Intended use(s):
The Optilite C1 Inactivator Kit is intended for the quantitative *in vitro* measurement of human C1 inactivator in human serum using the Binding Site Optilite analyzer. Measurement of C1 inactivator levels in serum is an aid in the diagnosis of hereditary angioedema (HAE) in conjunction with other laboratory and clinical findings
2. Indication(s) for use:
Same as Intended Use.
3. Special conditions for use statement(s):
Prescription use only

4. Special instrument requirements:

The Binding Site Optilite Analyzer (k110035)

I. Device Description:

The Optilite C1 Inactivator Kit is comprised of the following reagents: sheep antiserum for C1 Inactivator and is supplied in stabilized liquid form (preservatives: 0.099% sodium azide, 0.1% E-amino-n-caproic acid (EACA), 0.1% Ethylenediamine tetra-acetic acid (EDTA) and 0.01% benzamidine); calibrator and controls: pooled human serum, supplied in stabilized liquid form (contain 0.099% sodium azide, 0.1% EACA and 0.01% benzamidine as preservatives); reaction buffer: Containing 0.099% sodium azide as a preservative.

Materials required but not provided: Optilite Diluent 2: diluent containing 0.099% sodium azide as preservative

J. Substantial Equivalence Information:

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

Human C1 Inactivator Kit for use on SPAPLUS, k122304

2. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	Quantification of C1 inactivator in human serum. It is intended to aid in the diagnosis of hereditary angioedema in conjunction with other laboratory and clinical findings	Same
Assay type	Quantitative	Same
Test method	Immunoturbidimetry	Same
Specimen type	Serum	Same
Detection antibody	Sheep anti-human C1 inactivator	Same
Traceability	Calibrated against European Reference Material ERM – DA470k.	Same
Control	Two controls (provided): high (0.3 g/L) and low (0.15g/L)	Same
Expected value (adult)	0.21-0.38 g/L	Same
Open vial stability	3 months	Same
On-board stability	30 days	Same

Differences		
Item	Device	Predicate
Instrument	Optilite Analyzer	SPAPLUS Analyzer
Calibrator	One calibrator (provided): single calibrator of 0.0425 g/L and auto-diluted by Optilite analyzer	Six pre-diluted stabilized calibrator set (provided): 0.006, 0.01, 0.015, 0.02, 0.03, 0.04 g/L
Measuring range	0.08 – 0.44 g/L (1/5 dilution) 0.16 – 0.88 g/L (1/10 dilution)	0.06 – 0.40 g/L (1/10 dilution) 0.12 – 0.80 g/L (1/20 dilution)
Sample dilution	1:5 and 1:10	1:10 and 1:20

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP7-A2: Interference Testing in Clinical Chemistry, Approved Guideline – Second Edition

CSLI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

CLSI C28-A3: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory

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

Precision summary*							
Sample	Mean (g/L)	Within-Run CV%	Between-Run CV%	Between-day CV%	Between-Lot CV%	Between-Instrument CV%	Total CV%
Serum 1	0.127	1.9	5.7	4.7	0.06	2.5	7.6
Serum 2	0.165	3.2	4.1	4.9	1.6	2.5	7.1
Serum 3	0.289	1.7	2.3	4.3	1.4	2.0	5.1
Serum 4	0.393	1.6	1.9	4.4	1.5	3.3	5.1
Serum 5**	0.418	2.0	1.8	3.8	0.5	1.7	4.7

*For calculating SD, use: $SD = \text{mean} \times CV\%$

** performed at the 1:10 sample dilution

b. Linearity/assay reportable range:

Linearity across the assay range (0.08 – 0.44 g/L) was confirmed by testing a serum pool with high range concentrations up to 0.473 g/L. The samples were serially diluted 10 times (at 1:5) down to the lower measuring range (0.007 g/L). All testing were performed three times. The regression plot equations where y is the measured level of C1 Inactivator concentration and x the theoretical concentration is as follows: $y=0.961x + 0.01$ (g/L). $R^2=1.00$

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

The calibration of the assay is traceable to the international reference standard ERM-DA470k.

Stability:

Stability studies demonstrated the following claims:

- *Real-time stability* – Human C1 Inactivator Kit: 2-8°C for 3 months. Study is on-going.
- *Open-vial stability* - The Human C1 Inactivator Kit: 2 – 8°C for up to 3 months.
- *On-board stability* – The Human C1 Inactivator Kit: 8 – 12°C for 30 days.

d. Detection limit:

The detection limits were determined by testing 60 replicates of a blank sample, the lowest calibrator, and a sample with value close to the blank sample. The limit of blank claim for this assay is 0.05 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 0.564 g/L. The limit of quantitation is defined as the lowest amount of analyte that can be quantitatively determined and has been estimated as 0.08 g/L for this assay.

e. Analytical specificity:

Interference by endogenous and other substances:

No significant assay interference effects were observed when tested with triglyceride (10 g/L), bilirubin (200 mg/L) or hemoglobin (5 g/L). Intralipid at 2.5 g/L showed signs of interference and lipemic samples are known to interfere with this assay. Therefore, lipemic samples should not be analyzed using this assay

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”.

In addition, no significant interference was observed with any of the 11 commonly used therapeutic drugs tested at the concentrations listed below:

Drug	Concentration tested
Acetaminophen	1324 µmol/L
Salicylic Acid	3.63 mmol/L
Ibuprofen	2425 µmol/L
Ascorbic Acid	342 µmol/L
Caffeine	308 µmol/L
Penicillin	75 mg/L
Digoxin	7.8 nmol/L
Cimetidine	79.2 µmol/L
Theophylline	222 µmol/L
Phenytoin	198 µmol/L
Furosemide	90 µmol/L

Hook Effect

No antigen excess was observed up to a level of 4.7 times the top of the calibration curve at the standard 1/5 sample dilution. This is equivalent to 1.8 g/L.

f. Assay cut-off:

Not determined

2. Comparison studies:

a. Method comparison with predicate device:

A total of 223 serum samples with C1 inactivator concentrations ranged from 0.071 to 0.666 g/L were assayed in singleton by both the Human C1 Inactivator Kit on TBS Optilite Analyzer and on the SPAPLUS Analyzer. The serum samples included 22 normal donors and 221 clinical samples (24 HAE and Inflammatory conditions); 177 IgG kappa paraprotein and unknown diagnosis). Regression equations were as follows:

Regression Fit	Regression Equation	Slope (95% CI)	Intercept (95% CI)
Passing-Bablok	$y = 0.92x + 0.01$	0.92 (0.89-0.95)	0.01 (0.01-0.02)
Weighted Deming	$y = 0.92x + 0.01$	0.92 (0.90-0.94)	0.01 (0.01-0.02)

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not determined

b. Clinical specificity:

Not determined

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Based on lower limit of reference range which is 0.21 g/L.

5. Expected values/Reference range:

The ranges provided were established from a limited number of samples and are intended for guidance purposes only. Expected values may vary with age, sex, sample type, diet and geographical location. Each laboratory should verify the transferability of the expected values to its own population and, if necessary, determine its own reference interval.

Adult serum range

	Number (n)	Mean (g/L)	Median (g/L)	95 Percentile range (g/L)
C1 Inactivator	120	0.30	0.30	0.21 – 0.38

N. Instrument Name:

The Binding Site Optilite® Analyzer

O. System Descriptions:

1. Modes of Operation:

Benchtop fully automated batch and random access analyzer

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes or No

3. Specimen Identification:

Barcode or manual entry

4. Specimen Sampling and Handling:

Specimen tubes or cups are manually loaded into sample racks. During testing specimens are sampled and diluted by the onboard pipetting system.

5. Calibration:

Analyzer software contains assay specific calibration program using assay specific calibrators.

6. Quality Control:

Analyzer software contains assay specific quality control program using assay specific quality control materials. Analyzer labeling recommends that quality control be performed daily.

P. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

Q. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.