

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

A. 510(k) Number:

K150658

B. Purpose for Submission:

New device

C. Measurand:

Kappa (κ) free light chains

Lambda (λ) free light chains

D. Type of Test:

Turbidimetry, quantitative

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Optilite® Freelite® Kappa Free Kit

Optilite® Freelite® Lambda Free Kit

G. Regulatory Information:

1. Regulation section:

21 CFR§866.5550 – Immunoglobulin (light chain specific) immunological test system

2. Classification:

Class II

3. Product code:

DFH, Kappa, antigen, antiserum, control

DEH, Lambda, antigen, antiserum, control

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

The Optilite Freelite Kappa Free Kit is intended for the quantitative in vitro measurement of kappa free light chains in serum using the Binding Site Optilite turbidimetric analyser. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinaemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings.

The Optilite Freelite Lambda Free Kit is intended for the quantitative in vitro measurement of kappa free light chains in serum using the Binding Site Optilite turbidimetric analyser. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinaemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings.

2. Indication(s) for use:

Same as intended use

3. Special conditions for use statement(s):

For prescription use only.

Warning: The kappa free light chain results for a given specimen determined with assays from different manufacturers or on different systems can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the kappa free light chain assay used. Values obtained with different assays or systems cannot be used interchangeably. If, in the course of serially monitoring a patient, the assay or system used for determining kappa free light chain levels is changed, additional sequential testing should be carried out. Prior to changing assay or system, the laboratory **MUST** confirm baseline values for patients being serially monitored.

Warning: The lambda free light chain results for a given specimen determined with assays from different manufacturers or on different systems can vary due to differences in assay methods and reagent specificity. The results reported by the

laboratory to the physician must include the identity of the lambda free light chain assay used. Values obtained with different assays or systems cannot be used interchangeably. If, in the course of serially monitoring a patient, the assay or system used for determining lambda free light chain levels is changed, additional sequential testing should be carried out. Prior to changing assay or system, the laboratory **MUST** confirm baseline values for patients being serially monitored.

4. Special instrument requirements:

Optilite® Analyzer (K141100)

I. Device Description:

The Optilite® Freelite® Kappa Free Kit and Optilite® Freelite® Lambda Free Kit are comprised of the following reagents:

- Latex Reagent: Consisting of polyclonal monospecific antibody coated onto polystyrene latex. Supplied in stabilized liquid form. Preservatives: 0.1% E-amino-n-caproic acid (EACA), 0.01% benzamidine, 0.05% ProClin.
- Calibrator and Controls: Pooled human serum, supplied in stabilized liquid form. Containing 0.099% sodium azide, 0.1% EACA and 0.01% benzamidine as preservatives.
- Reaction Buffer: Containing 0.099% sodium azide as a preservative.

J. Substantial Equivalence Information:

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

Freelite® Human Kappa Free kit for use on Roche Cobas Integra® 400/400*plus* (K070900)

Freelite® Human Lambda Free kit for use on Roche Cobas Integra® 400/400*plus* (K070900)

2. Comparison with predicate:

Similarities		
Item	Device Optilite® Freelite® Kappa Free Kit and Optilite® Freelite® Lambda Free Kit	Predicate Freelite® Human Kappa Free Kit and Freelite® Human Lambda Free Kit
Intended use	Quantitative in vitro measurement of kappa free light chains (FLC) or lambda FLC in serum	Same

Similarities		
Item	Device Optilite® Freelite® Kappa Free Kit and Optilite® Freelite® Lambda Free Kit	Predicate Freelite® Human Kappa Free Kit and Freelite® Human Lambda Free Kit
Indication for use	Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinaemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings.	Same
Analyte	Kappa: Kappa FLC Lambda: Lambda FLC	Same
Measurement	Quantitative	Same
Detection Method	Turbidimetric	Same
Sample type	Serum	Same
Detection Antibody	Kappa: Polyclonal sheep anti-human kappa antibody (F(ab) ₂ fragment) coated onto latex particles Lambda: Polyclonal sheep anti-human lambda antibody (F(ab) ₂ fragment) coated onto latex particles	Kappa: Same Lambda: Same
Open Vial Stability	3 months	Same
Reference Interval	Kappa: 3.30–19.40 mg/L Lambda: 5.71–26.30 mg/L Ratio: 0.26–1.65 mg/L	Same
Lambda Sample dilutions	Lambda: 1+1, 1+7, 1+79, 1+799, 1+7999	Same
Lambda Measuring Range (mg/L)	Lambda: At 1+ 7 standard dilution: 52–1390 mg/L Extended Measuring range: 1.3–34.7 mg/L (1+1)	Same

Similarities		
Item	Device Optilite® Freelite® Kappa Free Kit and Optilite® Freelite® Lambda Free Kit	Predicate Freelite® Human Kappa Free Kit and Freelite® Human Lambda Free Kit
	52–1390 mg/L (1+79) 520–13900 mg/L (1+799) 5200–139000 mg/L (1+7999)	

Differences		
Item	Device Optilite® Freelite® Kappa Free Kit and Optilite® Freelite® Labmda Free Kit	Predicate Freelite® Human Kappa Free Kit and Freelite® Human Lambda Free Kit
Instrument	Binding Site Optilite	Roche Cobas Integra® 400/400 <i>plus</i>
Kappa Sample dilutions	Kappa: 1+1, 1+9, 1+99, 1+999	Kappa: 1+1, 1+9, 1+99
Kappa Measuring Range (mg/L)	Kappa: At 1+9 Standard Dilution” 2.9–127 mg/L Extended Measuring range: 0.6–25.3 mg/L (1+1) 29–1270 mg/L (1+99) 290–12700 mg/L (1+999) 1450–63500 mg/L (1+4999)	Kappa: At 1+9 Standard Dilution” 2.9–127 mg/L Extended Measuring range: 0.6–25.3 mg/L (1+1) 29–1270 mg/L (1+99)
On-board Stability	30 days	3 months
Open Vial Stability	12 weeks	3 months

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

CLSI EP05-A2 “Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition”.

CLSI EP06-A “Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline”.

CLSI EP07-A2 “Interference Testing in Clinical Chemistry, Approved Guideline - Second Edition”.

CLSI 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 concentration of the soluble antigen is assessed by turbidimetry. The test sample is added to a solution containing the appropriate antibody in a reaction cuvette. A beam of light is passed through the cuvette and is increasingly scattered by the formation of insoluble immune complexes. Light scatter is monitored by measuring the decrease in intensity of the incident beam of light. The antibody in the cuvette is in excess so the amount of immune complex formed is proportional to the antigen concentration. A series of calibrators of known antigen concentration are assayed to produce a calibration curve of measured light scatter versus antigen concentration. Samples of unknown antigen concentration can then be assayed and the results read from the calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The precision studies were based on CLSI EP5-A2, where eight serum samples were evaluated with both assays. The samples chosen covered the assays’ measuring ranges: two samples were close to the low medical decision points (Kappa: 2.48 mg/L and 4.13 mg/L, Lambda: 4.28 mg/L and 7.14 mg/L), one sample was a negative (healthy) sample with a concentration within the reference range (Kappa: 8 mg/L, Lambda: 13 mg/L), two samples were close to the high medical decision points (Kappa: 14.55 mg/L and 24.25 mg/L, Lambda: 19.73 mg/L and 32.88 mg/L), and three samples were highly elevated clinical samples (both Kappa and Lambda: 75 mg/L, 110mg/L and 400 mg/L)) were tested in two runs per day (in duplicate) over 21 days using three analyzers. Samples were run at the standard dilution (1+9 for Kappa and 1+7 for Lambda) unless otherwise indicated. Results met the sponsor’s pre-determined acceptance criteria for total precision (%CV<8.5%), within-run precision (%CV<5%), between-run precision (%CV<8.5%), between-day precision (%CV<8.5%) and between-instrument precision (%CV<10%).

Optilite® Freelite® Kappa Free Kit

Kappa FLC	N	Mean g/L	Within-Run		Between-Run		Between-Day		Between-Instrument		Total Precision	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
1*	84	2.5	0.1	2.6	0.00	0.8	0.1	3.5	0.1	4.1	0.1	4.4
2	84	4.9	0.1	2.6	0.1	2.9	0.3	6.6	0.1	2.4	0.4	7.7

Kappa FLC	N	Mean g/L	Within-Run		Between-Run		Between-Day		Between-Instrument		Total Precision	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
3	84	8.2	0.2	2.1	0.1	1.7	0.3	4.1	0.2	2.7	0.4	5.0
4	84	13.7	0.2	1.7	0.1	1.0	0.6	4.0	0.4	3.2	0.6	4.5
5	84	23.2	0.3	1.5	0.4	1.8	0.6	2.7	0.5	2.2	0.8	3.5
6	84	71.8	2.4	3.3	1.3	1.8	2.1	3.0	1.6	2.3	3.4	4.8
7	84	105.1	5.5	5.2	0.0	0.0	4.5	4.2	4.1	3.9	7.1	6.7
8**	84	329.8	13.3	4.0	5.7	1.7	13.2	4.0	5.4	1.6	19.6	5.9

*performed at the 1+1 sample dilution

**performed at the 1+99 sample dilution

Optilite® Freelite® Lambda Free Kit

Lambda FLC	N	Mean g/L	Within-Run		Between-Run		Between-Day		Between-Instrument		Total Precision	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
1*	84	4.7	0.1	2.1	0.1	2.7	0.2	3.2	0.1	3.0	0.2	4.7
2	84	7.5	0.2	3.0	0.3	3.7	0.5	7.2	0.67	8.6	0.7	8.6
3	84	14.4	0.2	1.6	0.2	1.5	0.5	3.2	0.5	3.6	0.6	3.9
4	84	19.8	0.4	1.8	0.4	2.0	0.4	2.1	0.5	2.9	0.7	3.4
5	84	30.0	0.6	2.0	0.5	1.8	0.8	2.6	0.9	2.9	1.1	3.7
6	84	71.1	1.3	1.8	1.5	2.0	1.7	2.4	1.3	1.8	2.6	3.6
7	84	115.6	4.0	3.4	4.9	4.2	5.3	4.6	3.2	2.7	8.2	7.1
8**	84	335.4	4.6	1.4	10.7	3.2	15.4	4.6	18.3	5.4	19.2	5.8

*performed at the 1+1 sample dilution

**performed at the 1+79 sample dilution

Reagents used in the Optilite® Freelite® Kappa and Lambda Free Kits are identical to those of the predicate device. Lot-to-lot studies were previously conducted in K070900.

b. Linearity/assay reportable range:

A linearity study was performed following CLSI EP06-A. The linearity of this assay has been confirmed using a full range pool spanning the claimed measuring range and a low range pool covering the normal range. These samples were serially diluted to cover the range at the standard dilution (1+9 for Kappa and 1+7 for Lambda).

Samples were run in triplicate. The linearity of the Optilite® Freelite® Kappa Kit was confirmed using serially diluted serum samples spanning the range of 2.9–127 mg/L with deviation from linearity <10%. The linearity of the Optilite® Freelite® Lambda Free Kit was confirmed using a serially diluted serum samples spanning the range of 5.2–139 mg/L with deviation from linearity <10%.

Kit	Assay reportable range Standard Dilution	Assay reportable range Expanded dilutions
Optilite® Freelite® Kappa Free Kit	2.9–127 mg/L	0.6–63500 mg/L
Optilite® Freelite® Lambda Free Kit	5.2–139 mg/L	1.3–39000 mg/L

For each sample pool, the mean observed value was also plotted against the calculated concentrations, and the relationship between the two was determined by both ordinary and weighted linear regression. Regression equations for the Optilite® Freelite® Kappa Free Kit and Optilite® Freelite® Lambda Free Kit high/full linear range and for the low linear range are as follows:

Analyte	Pool series	Sample Range (g/L)	Ordinary Linear Regression equation	Weighted Linear Regression equation	R
Kappa FLC	Full Range Pool	2.55–140.34	$y = 1.00x + 0.00$	$y = 1.01x - 0.09$	0.99
	Low Range Pool	2.60–40.7	$y = 1.00x + 0.00$	$y = 0.99x + 0.12$	0.99
Lambda FLC	Full Range Pool	4.33–155.45	$y = 1.00x - 0.00$	$y = 1.01x - 0.17$	0.99
	Low Range Pool	4.09–46.94	$y = 1.00x - 0.00$	$y = 1.00x + 0.02$	0.99

The approximate measuring range of the Optilite® Freelite® Kappa Free Kit at the standard dilution (1+9) is 2.9–127 mg/L.

The approximate measuring range of the Optilite® Freelite® Lambda Free Kit at the standard dilution (1+7) is 5.2–139 mg/L.

Antigen Excess:

Prozone/Hook effect parameters are in effect to protect the Optilite® analyzer from antigen excess effects. A sample with atypical reaction kinetics will have a ‘Prozone detected’ flag (prozone warning) in the results entry and the sample will be automatically re-measured at a higher analyzer dilution.

To test this warning system, reaction kinetics of normal and high level clinical samples were tested. No samples within the normal range produced false prozone detection warnings. All samples exceeding the measuring range gave either a ‘greater

than' or 'prozone detected' flag and the sample was automatically rerun at the next appropriate dilution.

Because the possibility of antigen excess can never be completely excluded and to address the potential for monoclonal samples to exhibit non-linearity, the following warning statement is included in the reagent package inserts:

Important Note: No automated check will identify all cases of antigen excess and a very small percentage of samples in antigen excess have normal reaction kinetics so will not prompt the "Prozone Detected" flag. It is recommended that the following statement accompany all free light chain results.

"Undetected antigen excess is a rare event but cannot be excluded. If these free light chain results do not agree with other clinical or laboratory findings, or if the sample is from a patient that has previously demonstrated antigen excess, the result must be checked by retesting at a higher sample dilution. Results should always be interpreted in conjunction with other laboratory tests and clinical evidence; any anomalies should be discussed with the testing laboratory."

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

Traceability:

In the absence of an international reference standard, the calibration of the assay is traceable to an internally assigned master calibrator.

Kit Stability:

Real-time stability: Studies to establish shelf-life stability (from the date of manufacture when stored at recommended temperature 2–8°C) of the predicate devices were carried out between 2008 and 2010. The reagents in the Optilite® Freelite® Kappa and Lambda Free kits are identical to those in the predicate devices; the predicate stability claim was able to be transferred. Data supports an 18-month stability claim.

Open-vial stability: Open vial stability claims from the predicate were revalidated on the Optilite® analyzer. The Optilite® Freelite® Kappa and Lambda Free Kit reagents can be stored opened at 2–8°C for up to 12 weeks.

On-board stability: On-board stability claims from the predicate were revalidated on the Optilite® analyzer. The Optilite® Freelite® Kappa and Lambda Free Kit reagents can be stored on-board the Optilite® Analyzer for 30 days.

d. *Detection limit:*

The analytical sensitivity of both kits was determined in accordance with CLSI EP17-

A. The Limit of Blank (LoB) was based on 60 determinations of a sample containing analyte depleted serum and sample diluent and was estimated as the 95% percentile of the distribution. The Limit of Detection (LoD) was calculated according to the equation $LoD = LoB + 1.645 \times SDs$ where SDs, the standard deviation was based on 12 determinations each of five LoQ samples with analyte levels near the lower limit of the reportable range. Total error (0.29 mg/L for Kappa and 0.17 mg/L for Lambda) at LoQ was within the sponsor's pre-determined criteria for maximum allowable total error.

Optilite® Freelite Assay	LoB	LoD	LoQ
Kappa Free Kit	0.100 mg/L	0.158 mg/L	0.580 mg/L
Lambda Free Kit	0.185 mg/L	0.274 mg/L	1.300 mg/L

e. *Analytical specificity:*

Interferences were assessed according to CLSI EP7-A2 by testing six serum samples for each assay with Kappa FLC and Lambda FLC concentrations falling below (deficient), within (healthy), above (elevated) or close to the limits of the reference interval. Each sample was spiked with interfering substances and tested in a minimum of three replicates. For non-interference to be claimed, the mean results from the spiked samples must be within 10% of the mean of the control samples.

Kappa results: The data demonstrated that the assay was not affected by the following substances at the concentrations given below.

Lambda results: The data demonstrated that the assay was not affected by the following substances at the concentrations given below.

Category	Interferent	Optilite® Freelite® Kappa Free Kit	Optilite® Freelite® Lambda Free Kit
		Concentration tested	Concentration tested
Endogenous Substances	Bilirubin	200 mg/L	200 mg/L
	Hemoglobin	0.625 g/L*	5 g/L
	Intralipid	62.5 mg/dL*	1000 mg/dL
	Triglyceride	1000 mg/dL	2000 mg/dL
OTC Drugs	Acetaminophen	1324 µmol/L	1324 µmol/L
	Acetylsalicylic acid	3.63 µmol/L	3.63 µmol/L
	Ascorbic acid	342 µmol/L	342 µmol/L
	Caffeine	308 µmol/L	308 µmol/L
	Ibuprofen	1212.5 µmol/L	2425 µmol/L
Common Drugs	Cimetidine	79.2 µmol/L	79.2 µmol/L
	Digoxin	7.8 nmol/L	7.8 nmol/L

Category	Interferent	Optilite® Freelite® Kappa Free Kit	Optilite® Freelite® Lambda Free Kit
		Concentration tested	Concentration tested
	Penicillin	75 mg/L	75 mg/L
	Phenotoin	198 µmol/L	198 µmol/L
	Theophylline	222 µmol/L	222 µmol/L
Specific Drugs	Bortezomib	6 mg/mL	3 mg/mL
	Cyclophosphamide Monohydrate	60 µg/mL	60 µg/mL
	Pomalidomide	100 µg/mL	100 µg/mL
	Prednisolone	100 µg/mL	100 µg/mL

*Hemoglobin and Intralipid passed at very low interferent concentrations. The Optilite® Freelite® Kappa Free Kit is therefore not suitable for use with hemolyzed or lipemic samples. This is clearly stated in the product insert.

f. *Assay cut-off:*

See expected values/reference range.

2. Comparison studies:

a. *Method comparison with predicate device:*

The Binding Site Optilite FREELITE™ assays for Kappa and Lambda were evaluated and compared to the results obtained with the kits on the predicate analyzer. A total of 292 serum samples spanning the dynamic range of one or both assays were used in this study; 238 of these samples were run on the Kappa assays, 192 were run on the Lambda assays, 143 of these samples were run on both Kappa and Lambda assays. Samples were tested in singlicate. Samples included nine normal donors and 74 clinical samples with relevant admission diagnosis (including multiple myeloma, Waldenström's Macroglobulinemia, lymphocytic neoplasms and systemic lupus erythematosus). The remainder of samples had unknown clinical status.

Analyte	N	Sample Range (g/L)	Passing Bablok Regression equation	Slope (95% CI)	Y-Intercept (95% CI)	R ²
Kappa FLC	238	3.42 – 45578.13	$y = 0.95x - 0.74$	0.95 (0.92 to 0.97)	-0.74 (-1.29 to -0.18)	0.979
Lambda FLC	192	1.91 – 5089.37	$y = 1.01x + 0.39$	1.01 (0.98 to 1.03)	0.39 (0.03 to 0.84)	0.981
κ/λ FCL Ratio	143	0.002 – 603.42	$y = 0.88x + 0.02$	0.88 (0.84 to 0.93)	0.02 (-0.03 to 0.05)	0.991

b. Matrix comparison:

Not applicable

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. See assay cut-off.

5. Expected values/Reference range:

The reference ranges were transferred from the predicate devices and were verified by testing 50 adult donor samples.

Kappa FLC reference range: 3.30–19.40 mg/L

Lambda FLC reference range: 5.71–26.30 mg/L

Kappa/Lambda Ratio reference Range: 0.26–1.65 mg/L

In the product insert, the sponsor recommends that each user of the kit should verify the transferability of the expected values to its own population and if necessary determine its own reference interval.

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.