

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

A. 510(k) Number:

K173732

B. Purpose for Submission:

Modified IVD assay on previously cleared instrument

C. Measurand:

Kappa (κ) free light chains and Lambda (λ) free light chains

D. Type of Test:

Quantitative, Turbidimetry

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Optilite Freelite Mx Kappa Free Kit
Optilite Freelite Mx Lambda Free Kit

G. Regulatory Information:

1. Regulatory 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:

The Optilite Freelite Mx Kappa Free Kit is intended for the quantitative in vitro measurement of Kappa free light chains in serum and urine using the Binding Site Optilite analyzer. 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 Mx Lambda Free Kit is intended for the quantitative in vitro measurement of Lambda free light chains in serum and urine using the Binding Site Optilite analyzer. 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 for use:

Same as intended use.

3. Special conditions for use statement:

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 (Indiko) (K110035)

I. Device Description:

The Optilite Freelite Mx Kappa Free Kit is comprised of the following reagents:

- Latex Reagent: Sheep anti-Human Kappa (polyclonal monospecific) antibody (F(ab')₂ fragment) bound to 200nm polystyrene latex particles. In 0.033M Glycine buffered saline pH8 (containing Sodium Azide (0.033%), Proclin (0.05%), Benzamidine (0.01%) and EACA (0.1%) as preservative plus BSA (0.033%))
- 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.

The Optilite Freelite Mx Lambda Free Kit is comprised of the following reagents:

- Latex Reagent: Sheep anti-Human Lambda (polyclonal monospecific) Free antibody (F(ab')₂ fragment) bound to 200nm polystyrene latex particles. In 0.033M Glycine buffered saline pH8 (containing Sodium Azide (0.033%), Proclin (0.05%), Benzamidine (0.01%) and EACA (0.1%) as preservatives plus BSA (0.1665%))
- 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.

Note - In Optilite Freelite kits, the latex reagent and reaction buffer are supplied in a single wedge with a chamber for each fluid. They are therefore labelled as a single component Optilite Kappa Free Mx Reagent or Optilite Lambda Free Mx Reagent.

J. Substantial Equivalence Information:

1. Predicate device name:

Freelite Human Kappa Free Kit and Freelite Human Lambda Free Kit for use on Siemens BNII

2. Predicate 510(k) number:

K040009

3. Comparison with predicate:

Similarities		
Item	Device Optilite Freelite Mx Free Kit	Predicate Freelite Human Free Kit (K040009)
Intended Use (Kappa)	Quantitation of kappa free light chains in serum and urine. It is intended to aid 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
Intended Use (Lambda)	Quantitation of lambda free light chains in serum and urine. It is intended to aid 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 Free Light Chain Lambda Free Light Chain	Same
Assay Format	Quantitative	Same

Similarities		
Item	Device Optilite Freelite Mx Free Kit	Predicate Freelite Human Free Kit (K040009)
Detection Antibody	LK016.M.OPT.A: Sheep anti-human kappa antibody (F(ab)2 fragment) bound to latex particles LK018.OPT.A: Sheep anti-human kappa antibody (F(ab)2 fragment) bound to latex particles	Same
Calibration	The Optilite analyzer produces a calibration curve by performing multiple dilutions of a single calibrator fluid	Same
Traceability	Internally produced master calibrator	Same
Sample matrix	Serum and urine	Same
Open vial stability	3 months	Same

Differences		
Item	Device Optilite Freelite Mx Free Kit	Predicate Freelite Human Free Kit (K040009)
Instrument	Optilite	Siemens BNII
Test Method	Turbidimetric	Nephelometric
Adult Reference Interval	Free Kappa: 32.90 mg/L [#] Free Lambda: 3.79 mg/L [#]	Free Kappa: 1.35–24.19 mg/L Free Lambda: 0.24–6.66 mg/L Kappa/Lambda Ratio: 2.04–10.37 Reference intervals taken from predicate product inserts.
Measuring Range and Dilutions (Kappa)	1/1: 0.3–12.65 mg/L 1/2: 0.6–25.3 mg/L 1/10: 2.9–127 mg/L* 1/100: 29–1270 mg/L 1/1000: 290–12700 mg/L 1/5000: 1450–63500 mg/L	1/1: 0.06–1.9 mg/L 1/5: 0.3–9.5 mg/L 1/20: 1.2–38 mg/L 1/100: 5.9–190 mg/L* 1/400: 23.6–760 mg/L 1/2000: 118–3800 mg/L 1/8000: 472–15200 mg/L
Measuring Range and Dilutions (Lambda)	1/1: 0.74–17.35 mg/L 1/2: 1.3–34.7 mg/L 1/8: 5.2–139 mg/L* 1/80: 52–1390 mg/L 1/800: 520–13900 mg/L 1/8000: 5200–139000 mg/L	1/1: 0.05–1.6 mg/L 1/5: 0.25–8.0 mg/L 1/20: 1.0–32.0 mg/L 1/100: 5.0–160 mg/L* 1/400: 20.0–640 mg/L 1/2000: 100–3200 mg/L 1/8000: 400–12800 mg/L
On Board Stability	30 days	None quoted

[#] 97.5th Percentile (one sided reference interval)

* Measuring range at standard dilution

K. Standard/Guidance Documents Referenced:

- CLSI EP17-A Protocols for Determination of Limits of Detection and Limit of Quantification; Approved Guideline
- CLSI EP7-A2 Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition
- CLSI EP6-A Evaluation of The Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP5-A2 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Second Edition

- CLSI EP28-A3c Defining, Establishing, And Verifying Reference Intervals in The Clinical Laboratory; Approved Guideline – Third Edition (formerly CLSI C28-A3c)

L. Test Principle:

Evaluating the concentration of a soluble antigen (e.g. Kappa free light chains) by turbidimetry involves the addition of the test sample to a solution containing the appropriate antibody in a reaction vessel or cuvette. A beam of light is passed through the cuvette and, as the antigen-antibody reaction proceeds, the light passing through the cuvette is scattered increasingly as insoluble immune complexes are formed. 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 initially 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:

1. Analytical performance: All results presented below met the manufacturer’s pre-determined acceptance criteria.

a. Precision/Reproducibility:

Kappa: The within-run, between-run, between-day and between-instrument precision were determined by testing four urine sample pools over 21 days with two runs per day using one reagent lot on three analyzers. Results are summarized below.

Sample	Mean (mg/L)	Within Run		Between Run		Between Day		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	5.49	0.28	5.1	0.10	1.8	0.30	5.4	0.35	6.3	0.42	7.6
2	33.08	0.70	2.1	1.61	4.9	2.08	6.3	0.55	1.7	2.72	8.2
3	99.16	3.12	3.1	4.56	4.6	4.29	4.3	2.62	2.7	6.99	7.1
4	179.12	5.16	2.9	5.11	2.9	13.89	7.8	12.88	7.2	15.68	8.8

Lambda: The within-run, between-run, between-day and between-instrument precision were determined by testing five urine sample pools over 23 days with two runs per day using one reagent lot on three analyzers. Results are summarized below.

Sample	Mean (mg/L)	Within Run		Between Run		Between Day		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	4.48	0.11	2.5	0.22	4.9	0.27	4.8	0.05	1.1	0.33	7.3
2	7.19	0.35	4.8	0.37	5.1	0.36	5.1	0.48	6.7	0.62	8.7
3	54.37	1.22	2.2	3.17	5.8	2.88	5.3	3.25	6.0	4.45	8.2
4	109.27	5.19	4.8	4.39	4.0	5.72	5.2	4.45	4.1	8.89	8.1
5	133.46	4.09	3.1	3.66	2.7	10.11	7.6	11.62	8.7	11.50	8.6

b. Linearity/assay reportable range:

A linearity study was performed following CLSI EP6-A. The linearity of the Kappa Free and Lambda Free assays was confirmed using serially diluted urine samples to cover the standard measuring ranges of 2.9–127mg/L (Kappa) and 5.2–139mg/L (Lambda) respectively. The results demonstrated that the kappa free and lambda free assays are linear over the ranges of 2.383–142.687mg/L (Kappa) and 3.87–160.02mg/L (Lambda) with deviation from linearity $\leq 10\%$.

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

Traceability: Internally produced master calibrator

Stability: On board, open vial and real time stability was evaluated in K150658.

d. Detection limit:

The analytical sensitivity was determined in accordance with CLSI EP17-A and was carried out using both serum and urine matrices. The Limit of Blank (LoB) was based on 60 determinations of blank samples (analyte depleted serum and urine at a low analyte concentration) and was estimated at the 95th percentile of the distribution. The Limit of Detection (LoD) was calculated from the LoB and the combined SD of the five Limit of Quantitation (LoQ) samples. The LoQ was calculated from five independent samples (serum samples: samples were diluted with analyte depleted serum; urine samples: in house urine samples at low analyte concentration were pooled with an in house urine with a higher analyte concentration) to achieve a concentration close to the bottom of the measuring range) tested twelve times over five days. The tabulated summary of results is shown below.

	LoB	LoD	LoQ
Kappa Free (Serum)	0.195mg/L	0.224mg/L	0.330mg/L
Kappa Free (Urine)	0.210mg/L	0.232mg/L	0.330mg/L
Lambda Free (Serum)	0.285mg/L	0.393mg/L	0.740mg/L
Lambda Free (Urine)	0.080mg/L	0.184mg/L	0.740mg/L

e. *Analytical specificity:*

Interference:

Interferences were assessed according to CLSI EP7-A2 by testing a single urine sample for the Kappa Free assay and the Lambda Free assay. Samples were prepared with an analyte concentration around the reference limit of each assay. Each sample was made up using urine from a healthy adult donor and urine from a kappa or lambda myeloma patient. Samples containing interferents were compared to matched control samples which contained no interferent. The mean results from the spiked samples must be within 10% of the mean of the control samples.

Kappa:

No significant assay interference effects were observed when the samples were tested with substances at the concentrations given below.

Substance	Concentration
Ascorbic Acid	200 mg/L
Albumin	5 g/L
Bilirubin	100 mg/L
Bortezomib	6 mg/mL
Cyclophosphamide	330 mg/mL
Digoxin	0.375 µg/mL
Haemoglobin	240 mg/L
Penicillin	75 mg/L
Phenytoin	15 mg/L
Theophylline	150 mg/L

Lambda:

No significant assay interference effects were observed when the samples were tested with substances at the concentrations given below.

Substance	Concentration
Ascorbic Acid	200 mg/L
Albumin	5 g/L
Bilirubin	100 mg/L
Bortezomib	3.6 mg/mL
Cyclophosphamide	330 mg/mL
Digoxin	0.375 µg/mL
Haemoglobin	250 mg/L
Penicillin	75 mg/L
Phenytoin	15 mg/L
Theophylline	150 mg/L

Cross reactivity:

No significant cross reactivity was observed during testing Freelite Human Kappa Free Kit and Freelite Human Lambda Free Kit for use on Siemens (K040009). The specificity of the antisera is unchanged.

Antigen Excess Detection:

The possibility of antigen excess occurring when using the device on the Optilite analyzer was evaluated in K150658.

f. Assay cut-off:

Not applicable. Refer to expected values of reference range.

2. Comparison studies:

a. Method comparison:

Kappa:

A comparison study was performed by analyzing 165 urine samples (including 86 with analyte levels below the reference limit) using the Optilite Freelite Mx Kappa Free kit and the predicate (K040009) assay. Passing Bablok regression analysis generated the following results:

$$y = 1.02x - 0.21 \text{ (mg/L)} \quad (y = \text{Optilite}; x = \text{predicate analyzer})$$

$$\text{correlation coefficient } r = 0.992$$

Lambda:

A comparison study was performed by analyzing 115 urine samples (including 59 with analyte levels below the reference limit) using the Optilite Freelite Mx Lambda Free kit and the predicate (K040009) assay. Passing Bablok regression analysis generated the following results:

$$y = 1.11x - 0.27 \text{ (mg/L)} \quad (y = \text{Optilite}; x = \text{predicate analyzer})$$

correlation coefficient $r = 0.947$

b. *Matrix comparison:*

Not applicable

3. Clinical studies:

a. *Clinical Sensitivity/clinical specificity:*

The reference interval limits were used for determination of positive and negative samples as below.

	Predicate (mg/L)	Test (mg/L)
Kappa Free	23	32.9
Lambda Free	2.18	3.79

Kappa:

A total of 170 samples were assayed using the test and predicate devices. Four (short volume or high activity) samples were excluded in the concordance analysis.

		Predicate Assay		
		Positive	Negative	Total
Test Assay	Positive	78	1	79
	Negative	8	79	87
	Total	86	80	166

Agreement	% Agreement	95% Confidence Interval
Positive	90.7%	82.7% to 95.2%
Negative	98.8%	93.3% to 99.8%
Overall	94.6%	90.0% to 97.1%

Lambda:

A total of 170 samples were assayed using the test and predicate devices. Two (short volume or high activity) samples were excluded in the concordance analysis.

		Predicate Assay		
		Positive	Negative	Total
Test Assay	Positive	56	0	56
	Negative	20	92	112
	Total	76	92	168

Agreement	% Agreement	95% Confidence Interval
Positive	73.7%	62.8% to 82.3%
Negative	100.0%	96.0% to 100.0%
Overall	88.1%	92.3% to 92.2%

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

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Normal adult urine	Mean (mg/L)	Median (mg/L)	Reference Limit (mg/L) 97.5 th Percentile
Kappa free	7.64	4.54	32.90
Lambda free	1.03	0.74	3.79

N. Proposed Labelling:

The labelling 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.