510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K250549

B Applicant

The Binding Site Group Ltd

C Proprietary and Established Names

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

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DFH, DEH	Class II	21 CFR 866.5550 - Immunoglobulin (Light Chain Specific) Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared device: Addition of intended use as an aid in the evaluation of Monoclonal Gammopathy of Undetermined Significance (MGUS) on Optilite Analyzer.

B Measurand:

Kappa (κ) Free Light Chain (FLC)
Lambda (λ) Free Light Chain (FLC)

C Type of Test:

Immunoturbidimetry; Quantitative

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for 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 in serum and urine aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE), and in serum aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted 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 in serum and urine aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE), and in serum aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted in conjunction with other laboratory and clinical findings.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Optilite Freelite Mx Kappa Free Kit
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.

Optilite Freelite Mx Lambda Free Kit
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.

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

Precaution:
Evaluation of monoclonal gammopathy of undetermined significance (MGUS):

- The performance has not been sufficiently studied in Light Chain MGUS patients.
- Patients with renal disease or inflammation may have elevated levels of kappa and lambda free light chains (FLC).
- Sample populations excluded MGUS populations that were further diagnosed with a disease/disorder in subsequent testing with another medical device such as neoplasia, and infectious diseases including human immunodeficiency virus. Thus, the specificity of the test may be inflated.
- The performance has not been fully evaluated on all race/ethnicity in the intended use population.

D Special Instrument Requirements:

Optilite Analyzer (K141100)

IV Device/System Characteristics:

A Device Description:

No modification is made to the kit components for the Optilite Freelite Kappa and Lambda Free Kits cleared in K173732 and K150658.

The assays are comprised of the following reagents:

- Latex Reagent: Consisting of polyclonal monospecific antibody coated onto polystyrene latex with preservatives, supplied in stabilized liquid form.
- Calibrator and Controls: Pooled human serum with preservatives, supplied in stabilized liquid form.
- Reaction Buffer: Containing 0.099% sodium azide as a preservative.

B Principle of Operation:

No modification is made to the principle of operation for the Optilite Freelite Mx Kappa and Optilite Freelite Mx Lambda Free Kits cleared in K173732 and K150658.

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. Samples of unknown antigen concentration can then be assayed, and the results read from the calibration curve.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Freelite Human Kappa Free Kit for use on the Siemens BN II
Freelite Human Lambda Free Kit for use on the Siemens BN II

B Predicate 510(k) Number(s):

K040009

C Comparison with Predicate(s):

Device & Predicate Device(s):	K250549 (Candidate Device)	K040009 (Predicate Device)
Device Trade Name	Optilite Freelite Mx Kappa Free Kit Optilite Freelite Mx Lambda Free Kit	Freelite Human Kappa/Lambda Free Kits for use on Siemens BNII
General Device Characteristic Similarities		
Intended Use/ Indications For 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 in serum and urine aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE); and in serum aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted 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 in serum and urine aids in the diagnosis and monitoring of multiple myeloma,	Freelite Human Kappa Free Kit This kit is intended for the quantitation of kappa free light chains in serum and urine on the Siemens BN™II. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus in conjunction with other laboratory and clinical findings. Freelite Human Lambda Free Kit This kit is intended for the quantitation of lambda free light chains in serum and urine on the Siemens BNII. Measurement of free light chains aids in the diagnosis and monitoring of

	lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE); and in serum aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted in conjunction with other laboratory and clinical findings.	multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus in conjunction with other laboratory and clinical findings.
Assay Type	Quantitative	Same
Test Method	Turbidimetry	Same
Samples	Serum and urine	Same
Detection Antibody	Kappa: Polyclonal sheep anti-human Kappa antibody coated onto latex particles Lambda: Polyclonal sheep anti-human Lambda antibody coated onto latex particles	Same
Reference Interval (Serum)	Kappa: 3.30–19.40 mg/L Lambda: 5.71–26.30 mg/L Ratio: 0.26–1.65	Same
Traceability	Internal reference material	Same
Open-vial Stability	3 months	Same
General Device Characteristic Differences		
Measuring range (at standard dilution)	Kappa: 2.9–127 mg/L (1/10) Lambda: 5.2–139 mg/L (1/8)	Kappa: 5.9– 190 mg/L (1/100) Lambda: 5.0–160 mg/L (1/100)
Reference Interval (Urine)	Kappa: 32.90 mg/L[*] Lambda: 3.79 mg/L[*]	Kappa: 1.35–24.19 mg/L[#] Lambda: 0.24–6.66 mg/L[#] Ratio: 2.04–10.37[#]

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

VI Standards/Guidance Documents Referenced:

Not applicable

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Refer to K173732 and K150658

2. Linearity:

   Refer to K173732 and K150658

3. Analytical Specificity/Interference:

   Refer to K173732 and K150658

4. Assay Reportable Range:

   Refer to K173732 and K150658

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Refer to K173732 and K150658

6. Detection Limit:

   Refer to K173732 and K150658

7. Assay Cut-Off:

   Refer to expected values/reference range below.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Refer to K173732 and K150658

2. Matrix Comparison:

   Not applicable

C Clinical Studies:

MGUS is a clinically asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder. The performance of the Optilite Freelite Mx Kappa and Optilite Freelite Mx Lambda Free Kits as an aid in the evaluation of MGUS was investigated from the following retrospective clinical studies:

Study 1:

A retrospective study was performed by testing a total of 229 samples from clinically confirmed MGUS patients (with 225 IFE positivity) and a total of 136 samples from clinically defined non-MGUS patients with polyclonal immunostimulation (confirmed with SIFE). Clinical diagnostic criteria and classification for MGUS and related plasma-cell disorders were, as practiced clinically, fulfilled, but were not limited to the criteria outlined by the 'International Myeloma

Working Group (IMWG)' consensus. The result of the device was compared to the clinical diagnosis for each sample.

The cohort of 229 MGUS samples included 173 non-IgM MGUS, 24 IgM MGUS, 10 light chain (LC) MGUS and 22 Biclonal. Out of 229 MGUS, 225 were IFE positive and four with no obvious paraprotein or unclear IFE result. However, these four IFE negative samples were categorized as LC-MGUS based on the positive clinical findings. All 229 samples were tested for FLC kappa and lambda levels with the Optilite Freelite Kappa and Lambda Free kits on the Optilite Analyzer. FLC κ/λ ratios were also calculated for each sample. The test result for MGUS positive or negative were based on the following FLC kappa and lambda levels criteria:

- For Non-LC MGUS, the test was considered as "MGUS Positive" or "Abnormal" when abnormal FLC κ/λ ratio (outside reference interval, i.e., <0.26 or >1.65) with IFE positivity was determined.
- For LC MGUS, the test was considered as "MGUS Positive" when abnormal FLC κ/λ ratio (outside reference interval, i.e., <0.26 or >1.65) with elevated FLC kappa (>19.40 mg/L) or elevated FLC lambda FLC (> 26.30 mg/L) was determined.

One hundred twenty-nine (129) out of 229 MGUS cases were tested positive by the Optilite Freelite Mx Kappa Free Kit and Optilite Freelite Mx Lambda Free Kit with a positive rate of 56.3% (95% CI: 49.6–62.9%). The distribution of the cohort and the positivity rate for each clinical type of MGUS are summarized in the following table:

MGUS Type	N	n (n/N%) Freelite positive
Non-IgM MGUS (all)	**173**	**95 (54.9%)**
IgG κ	74	47 (63.5%) >1.65
IgG λ	61	20 (32.8%) <0.26
IgA κ	21	15 (71.4%) >1.65
IgA λ	15	9 (60.0%) <0.26
IgD κ	0	0 (0%)
IgD λ	0	0 (0%)
Other *	2	0 (0%)
IgM MGUS (all)	**24**	**10 (41.7%)**
IgM κ	20	9 (45.0%)>1.65
IgM λ	4	1 (25.0%) <0.26
LC-MGUS (all)	**10**	**10 (100%)**
κ	5	5 (100%)
λ	5	5 (100%)
Biclonal	22	2 (9.1%) <0.26
TOTAL	**229**	**129 (56.3%)**

* λ band (not free light chain) with no obvious corresponding heavy chain. These samples have been categorized as non-IgM MGUS based on associated IFE and FLC results generated for these samples.

The 136 samples from patients with confirmed non-MGUS polyclonal stimulation (polyclonal hypergammaglobulinemia) were comprised of autoimmune diseases (27); diabetes (20); cardiovascular diseases (6); liver diseases (9); renal diseases (6); infection/inflammation (8); endocrine disorders (3); respiratory diseases (1); cancers (2); and other diseases/conditions (anemia, arthralgia, back pain, thigh pain, bone pain, elevated globulin levels, leg pain, low Hb, low sodium, macrocytosis, malaise, neutrophilia, night sweats, neutrophilia, poly arthropathy, thrombocytopenia, raised CRP, rash and itch, specific antibody deficiency, tired all the time (TATT), tiredness, weight loss, deranged liver enzymes) (54). Among 136 non-MGUS samples, 125 of these were determined as negative by the Optilite Freelite Mx Kappa Free Kit and Optilite Freelite Mx Lambda Free Kit, indicating a negative agreement of 91.9% (95% CI: 86.0–95.9%) in this sample cohort. The 11 false positive samples were from patients with the following disorders: diabetes (2); renal disease (1); infection/inflammation (1); liver diseases (1); autoimmune diseases (3); and other diseases/conditions (3).

Study 2:

Another retrospective study was performed by testing 49 subjects with clinically stable MGUS and four subjects with progressive clinical status converting from MGUS to multiple myeloma (MM). Among 49 MGUS stable subjects, 39 patients were diagnosed with non-IgM MGUS (20 IgG K, 14 IgG L, two IgA K, and three IgA L), and six patients with IgM MGUS (four IgM K and two IgM L) and four biclonal. All four subjects with progressive disease status were initially diagnosed with non-IgM MGUS (one IgG K, and three IgG L).

At least three serial draws were collected from each patient and tested with the Optilite Freelite Mx Kappa Free Kit and Optilite Freelite Mx Lambda Free Kit. FLC κ/λ ratio was calculated for each blood draw sample. Since the MGUS has been identified as a precursor to malignant diseases (multiple myeloma or amyloidosis), but not as a disease which requires treatment, no defined criteria in how to interpret consecutive FLC results are available. Therefore, for device evaluation purposes only, the criteria for stable MGUS and progressive MGUS based on test results in this study is defined as follows:

- FLC stable: Stable MGUS defined as < 25% increase in the concentration of the involved FLC in two assessments taken at least 6 months +/- 2 months apart where possible. This analysis included MGUS patients with and without abnormal FLC κ/λ ratio.
- FLC progressive: Progressive MGUS defined as the FLC κ/λ ratio outside of the reference interval of 0.26 –1.65, and an increase of ≥ 25% in the concentration of the involved light chain at or preceding the diagnosis of MM, compared to a previous sample taken at least 6 months +/- 2 months where possible.

Forty-three (43) out of 45 clinically stable MGUS subjects except LC MGUS, were determined as stable by the test and two out of four clinically progressive subjects were determined as progressive by these tests.

Limitations

- The performance has not been sufficiently studied in Light Chain (LC) MGUS patients – 10 LC MGUS patient samples were tested in Study 1, no LC MGUS patient samples were tested in Study 2.

- The performance has not been fully evaluated on all race/ethnicity in the intended use population.
- The study included time points of blood draws not indicative of clinical practice. The algorithm using only FLC has not been validated for progression of disease. Furthermore, a small sample size (4 patients) with only one specific subtype (i.e., IgG MGUS only) was used to study progression in Study 2. Risk mitigation strategies include that this test is not a stand-alone test for the evaluation of patients with MGUS and the test is to be utilized in conjunction with serum protein electrophoresis and immunofixation blood tests.

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Refer to K150658

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

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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