510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193047

B Applicant

Siemens Healthcare Diagnostics Products GmbH

C Proprietary and Established Names

N Latex FLC kappa, N Latex FLC lambda

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 BN systems

B Measurand:

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

C Type of Test:

Nephelometry, quantitative

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

N Latex FLC kappa and lambda are in-vitro diagnostic reagents for the quantitative determination of free light chains (FLC), type kappa or type lambda in human serum and EDTA-plasma. N Latex FLC kappa and lambda assays are used:

- as an aid in the diagnosis and monitoring of multiple myeloma (MM) on the BN Systems and Atellica CH Analyzer,
- as an aid in the diagnosis of amyloidosis (AL) on the BN Systems and Atellica CH Analyzer,
- as an aid in the evaluation of Monoclonal Gammopathy of Undetermined Significance (MGUS) on the BN Systems.

Results of FLC 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

Warning: The result of the FLC Kappa or FLC Lambda in a given specimen determined with assays and or instrument platforms from different manufacturers 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 FLC Kappa or FLC Lambda assay used. Values obtained with different assay methods cannot be used interchangeably.

Precaution:

- The performance of the N Latex FLC kappa and lambda has not been thoroughly studied in IgM and Light Chain MGUS patients due to the low prevalence of these subtypes.
- Patients with decreased renal function may have elevated FLC Kappa and FLC Lambda.
- Sample populations excluded MGUS populations that were further diagnosed with a disease/disorder in subsequent testing with another medical device such as human immunodeficiency virus, hepatitis, and chronic lymphocytic leukemia. Thus, because the samples were enriched the specificity of the test may be inflated.

D Special Instrument Requirements:

BN II (K943997) and BN ProSpec Systems (K001647)

IV Device/System Characteristics:

A Device Description:

No modification is made to the kit components for the N Latex FLC kappa and N Latex FLC lambda cleared in K171742 and K182098. The assays are comprised of the following reagents in liquid form:

- N latex FLC reagents: Consist of suspension of polystyrene particles coated with monoclonal antibodies (mouse) to either human FLC Kappa or human FLC Lambda; conjugate of S-adenosyl-cysteine/porcine thyreoglobin (<0.1 g/L); conjugate of S-adenosyl-L-homocysteine hydrolase (<100 U/mL); dithiothreitol (<0.5 g/L). Preservative: Sodium azide (<1 g/L)
- N FLC Supplementary Reagents A and B: N FLC Supplementary Reagent A contains mouse immunoglobulin in buffered solution and N FLC Supplementary Reagent B: consist of a buffered salt solution containing detergent. Preservatives in both Supplementary reagents: Sodium azide (<1 g/L).
- N FLC Standard SL: Contains human free light chains proteins, human serum albumin and protease inhibitors.
- N FLC Controls SL1 and SL2: contains human free light chain proteins, human serum albumin and protease inhibitors.

B Principle of Operation:

No modification is made to the principle of operation for the N Latex FLC kappa and N Latex FLC lambda cleared in K171742 and K182098.

The N Latex FLC kappa and lambda assays are based upon the principles of particle-enhanced immunoassay. Polystyrene particles coated with monoclonal antibodies to human free light chains, type kappa or lambda, respectively, are agglutinated when mixed with samples containing kappa and lambda free light chains. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Freelite Human Kappa And Lambda Free Kits For Use On The Dade Behring Nephelometer II

B Predicate 510(k) Number(s):

K031016

C Comparison with Predicate(s):

Device & Predicate Device(s):	K193047 (Device)	K031016 (Predicate)
Device Trade Name	N Latex FLC kappa N Latex FLC lambda	Freelite Human Kappa Free and Freelite Human Lambda Free kits on the Siemens BN II
General Device Characteristic Similarities		
Analyte	Kappa: Kappa FLC Lambda: Lambda FLC	Same
Measurement	Quantitative	Same
Detection Method	Nephelometric	Same
Calibrator	One level	Same
Reference Material	Internal Reference preparation	Same
Units	mg/L	Same
General Device Characteristic Differences		
Intended Use / Indications for Use	N Latex FLC kappa and lambda are in-vitro diagnostic reagents for the quantitative determination of free light chains (FLC), type kappa or type lambda in human serum and EDTA-plasma. N Latex FLC kappa and lambda assays are used: • as an aid in the diagnosis and monitoring of multiple myeloma (MM) on the BN Systems and Atellica CH Analyzer), • as an aid in the diagnosis of amyloidosis (AL) on the BN Systems and Atellica CH Analyzer, • as an aid in the evaluation of Monoclonal Gammopathy of Undetermined Significance (MGUS) on the BN Systems. Results of FLC measurements should always be interpreted in conjunction with other laboratory and clinical findings.	This kit is intended for the quantitation of kappa free light chains or lambda 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, Waldenstrom'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.
Sample Type	Serum and EDTA plasma	Serum and urine
Instrument System	Siemens BN II and BN ProSpec Systems	Siemens BN II

Detection Antibody	Kappa: Monoclonal mouse anti-human FLC kappa antibody onto polystyrene particles Lambda: Monoclonal mouse anti-human FLC lambda antibody onto polystyrene particles	Kappa: Polyclonal sheep anti-human kappa antibody coated onto latex particles Lambda: Polyclonal sheep anti-human lambda antibody coated onto latex particles
Analytical Measuring Ranges	Kappa: 3.4 – 110 mg/L Lambda: 1.9 – 60 mg/L	Kappa: 5.9 – 190 mg/L Lambda: 5.0 – 160 mg/L
Reference Interval	Kappa: 8.24 – 28.90 mg/L Lambda: 9.10 – 32.60 mg/L Ratio: 0.53 – 1.51	Kappa: 3.30 – 19.40 mg/L Lambda: 5.71– 26.30 mg/L Ratio: 0.26 – 1.65

VI Standards/Guidance Documents Referenced:

Not applicable

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   See K171742

2. Linearity:

   See K171742

3. Analytical Specificity/Interference:

   See K171742

4. Assay Reportable Range:

   See K171742

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

   See K171742

6. Detection Limit:

   See K171742

7. Assay Cut-Off:

   See expected values/reference range below.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   See K171742

2. Matrix Comparison:

   See K171742

C Clinical Studies:

Clinical performance of the N Latex FLC kappa assay and the N Latex FLC lambda assay as an aid in the diagnosis and monitoring of multiple myeloma, and as an aid in the diagnosis of amyloidosis was previously demonstrated in K171742 and K182098.

MGUS is a clinically asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder. The performance of the N Latex FLC kappa assay and the N Latex FLC lambda assay 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 121 samples from clinically confirmed MGUS patients (with IFE positivity) and a total of 102 samples from clinically defined non-MGUS patients with polyclonal immunostimulation (confirmed with SPEP/SIFE). The result of the device was compared to the clinical diagnosis for each sample.

The cohort of 121 MGUS samples included 89 Non-IgM MGUS, 21 IgM MGUS, and 11 light chain (LC) MGUS. All samples were tested for FLC kappa and lambda levels with N Latex FLC kappa and lambda assays on BN II analyzer. FLC κ/λ ratios were also calculated for each sample. The test result for MGUS positive or negative were based on the following 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., <0.53 or >1.51) 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., <0.53 or >1.51) with elevated FLC kappa (>28.9 mg/L) or elevated FLC lambda FLC (> 32.6 mg/L) was determined.

Sixty-one (61) out of 121 MGUS cases were tested positive by the N Latex FLC kappa and N Latex FLC lambda assay with a positive rate of 50.4% (95% CI: 41.2–59.6%). 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%) of MGUS Positive by N Latex FLC Assays
Non-IgM MGUS (All)	**89**	**43 (48.3%)**
IgG K	45	20 (44.4%)
IgG L	26	11 (42.3%)
IgG K/L (bi-clonal)	2	1 (50.0%)
IgA K	9	6 (66.7%)
IgA L	7	5 (71.4%)
IgD K	0	0 (0%)
IgD L	0	0 (0%)
IgM MGUS (All)	**21**	**8 (38.1%)**
IgM K	13	5 (38.5%)
IgM L	8	3 (37.5%)
LC MGUS (All)	**11**	**10 (90.9%)**
Kappa	6	5 (83.3%)
Lambda	5	5 (100.0%)
TOTAL	**121**	**61 (50.4%)**

The 102 samples from patients with confirmed non-MGUS polyclonal stimulation (polyclonal hypergammaglobulinemia) were comprised of chronic inflammation or infection (55); autoimmune diseases (12); cardiovascular diseases (13); cancer (4); liver diseases (2); respiratory diseases (5); GI related diseases (3); and other diseases/conditions (8). Ninety-two (92) out of 102 of these non-MGUS samples were also determined as negative by the N Latex FLC kappa and lambda assay, indicating a negative agreement of 90.2% (95% CI: 82.7–95.2%) in this sample cohort. The 10 false positive samples were from patients with the following disorders: polyclonal increase in the gamma globulin; Sjogren's syndrome; liver-related disease; hypervolemia; spinal cord injury; heart failure and nodular prostatic hyperplasia.

Limitation

In this study, sample populations excluded MGUS populations that were further diagnosed with a disease/disorder in subsequent testing with another medical device such as human immunodeficiency virus, hepatitis, and chronic lymphocytic leukemia. Thus, because the samples were enriched the specificity of the test in the study may be inflated. Risk mitigation strategies include use of the device in conjunction with other tests such as serum protein electrophoresis and immunofixation blood tests. The labeling also included this limitation.

Study 2:

Another retrospective study was performed by testing 61 subjects with clinically stable MGUS and four subjects with progressive clinical status converting from MGUS to multiple myeloma (MM). Among 61 MGUS stable subjects, 50 patients were diagnosed with non-IgM MGUS (33 IgG K, nine IgG L, six IgA K, and two IgA L), eight patients with IgM MGUS (seven IgM K and one IgM L), and three patients with LC MGUS (two kappa and one lambda). All four subjects with progressive disease status were initially diagnosed with non-IgM MGUS (one IgG K, one IgG L, one IgA K, and one IgA L).

At least four serial draws were collected from each patient and tested with the N Latex kappa and lambda assays. FLC κ/λ ratio was calculated for even blood draw samples. 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:

- For stable MGUS, FLC κ/λ ratio must be within the reference interval of 0.53 – 1.51 at the time of the last draw AND a relative change of the involved FLC (iFLC) is <25% for two consecutive assessments.
- For progressive MGUS, the FLC κ/λ ratio is outside of the reference interval (<0.53 or >1.51) AND a relative change of the involved FLC (iFLC) is ≥25% for two consecutive assessments.

Sixty (60) out of 61 clinically stable MGUS subjects were determined as stable by the test and three out of four clinically progressive subjects were determined as progressive by the test.

Limitation
The study included time points of blood draws not indicative of clinical practice. Also, the algorithm using only FLC had not been validated for progression of disease. Furthermore, a small sample size (4 patients) with only one subtype (i.e., non-IgM MGUS) was used to study progression in this study. 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:

See K171742

Kappa: 8.24 – 28.90 mg/L
Lambda: 9.10 – 32.60 mg/L
Ratio: 0.53 – 1.51

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.