510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K201496

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 monitoring of immunoglobulin light-chain amyloidosis (AL) on the BN System.

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 immunoglobulin light-chain amyloidosis (AL) on the BN Systems and Atellica CH Analyzer
- as an aid in the monitoring of immunoglobulin light-chain amyloidosis (AL) on the BN Systems
- 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. The values of FLC kappa or FLC lambda on BN Systems and on Atellica® CH Analyzer should not be used interchangeably.

If, in the course of serially monitoring a patient, the assay method used for determining the FLC kappa and FLC lambda levels is changed, additional sequential testing should be carried out. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.

Precaution:

- The performance of 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; K182098; and K193047. The assays are comprised of the following reagents in liquid form and ready-to-use:

- N latex FLC reagents: Consist of suspension of polystyrene particles coated with monoclonal antibodies (mouse) to either human FLC Kappa or human FLC Lambda with preservative.
- 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.
- 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; K182098 and K193047.

The N Latex FLC kappa and N Latex FLC 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 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 Free Kit and FREELITE Lambda Free Kit for use on the Dade Behring Nephelometer II

B Predicate 510(k) Number(s):

K031016

C Comparison with Predicate(s):

Device & Predicate Device(s):	K201496 (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 FLC; 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 immunoglobulin light-chain amyloidosis (AL) on the BN Systems and Atellica CH Analyzer, • as an aid in the monitoring of immunoglobulin light-chain amyloidosis (AL) on the BN Systems, • 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
Detection Antibody	Kappa: Monoclonal mouse anti-human FLC kappa antibody onto polystyrene	Kappa: Polyclonal sheep anti-human kappa antibody coated

	particles Lambda: Monoclonal mouse anti-human FLC lambda antibody onto polystyrene particles	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
Instrument System	Siemens BN II and BN ProSpec Systems	Siemens BN II
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 (MM), and as an aid in the diagnosis of immunoglobulin light-chain amyloidosis (AL) was previously demonstrated in K171742 and K182098; and as an aid in the evaluation of Monoclonal Gammopathy of Undetermined Significance (MGUS) was previously demonstrated in K193047.

The performance of the N Latex FLC kappa assay and the N Latex FLC lambda assay as an aid in monitoring of disease status in subjects diagnosed with AL was investigated in a clinical study using archived and prospective samples tested by the candidate devices in multicenter sites. A total of 111 AL subjects from four sites were enrolled in the study. Among them, 39 subjects were excluded (26 subjects did not return for follow-up or passed away; four subjects with wrong diagnosis; one subject not eligible; six subjects had no informed consent available; one subject with incorrect sample handling; and one subject with insufficient clinical information). The remaining 72 AL subjects with a total of 313 serum samples were used in the monitoring study analysis for analysis.

Of the 72 subjects, 19 subjects were diagnosis with Kappa AL and 53 with Lambda AL. Forty-six (46) subjects (64%) were male and 26 (36%) were female. The median age was 60 years old with the age ranging from 32 to 84 years. The majority of the race of subjects were European (n=58; 81%), 10 were U.S. Caucasian (14%) and the remaining four subjects were (5%) unknown. A total of 313 blood draws were collected from these 72 subjects. The median number of draws per subject was four, ranging from three to eight draws. The duration of the monitoring days ranged from 55 to 4033 days (with a median of 417 days).

The information collected for each sample included the following: (a) general information including patient's demographic information and date of blood sample collection; (b) clinical information including patient's diagnosis report/medical notes, treatment initiated, and diagnostic response criteria; c) laboratory data including serum/ urine electrophoresis results (M-protein), serum/ urine immunofixation electrophoresis.

To evaluate the clinical performance of N Latex FLC, the response criteria derived from N Latex FLC for each follow-up sample of each patient were compared to respective individual clinical status. Five response criteria: CR (Complete Response), VGPR (Very Good Partial Response), PR (Partial Response), SD/NR (Stable Disease/No response), PD (Progressive Disease) were

used to categorize each monitoring outcome for each patient based on the FLC Kappa and FLC Lambda results according to the following three therapy response evaluation criteria:

- **Evaluation Mode 1** based on National Comprehensive Cancer Network. "NCCN clinical practice guidelines in oncology (NCCN guidelines)." Systemic Light Chain Amyloidosis Version 1 (2022): 1–27.

- **Evaluation Mode 2** based on criteria established by Peter Mollee et al., (Mollee, P., et al. Evaluation of the N Latex light chain assay in the diagnosis and monitoring of AL amyloidosis, Clin Chem Lab Med 2013 (Dec); 15 (12):2303–10).

  Note: This publication emphasized that FLC methods can be used for monitoring if a dFLC value of at least 50 mg/L is reached. Therefore, the same criterion may be applied to detect recurrence (progression) of the disease.

- **Evaluation Mode 3** based on criteria established by G. Palladini, et al.[1, 2]
  1. Palladini, G., et al. (2019) When should treatment of AL amyloidosis start at relapse? Early, to prevent organ progression, Blood Adv. 3:212–215.
  2. Milani P., et al. (2018). Novel Therapies in Light Chain Amyloidosis. Kidney International Reports 3(3):530–541.

  Note: The publication evaluated the potential of low FLC levels and concluded that patients with initial dFLC values below 50 mg/L can be monitored and established a specific criterion for detecting a low-level response in the partial response categories.

All therapy response criteria based on above three Modes are summarized in the table below:

Response Criteria	Serum M Protein/ IFE	Evaluation Mode 1	Evaluation Mode 2	Evaluation Mode 3
CR, aCR*	Serum and urine IFE negative	FLC levels and ratio normal	FLC levels and ratio normal	FLC levels and ratio normal
VGPR		Reduction in the dFLC to <40 mg/L	Reduction in the dFLC to <40 mg/L	Reduction in the dFLC to <40 mg/L
PR		dFLC > 50 mg/L A greater than 50% reduction in the initial dFLC value	dFLC > 50 mg/L A greater than 50% reduction in the initial dFLC value	dFLC > 50 mg/L 1. A greater than 50% reduction in the initial dFLC value 2. For patients with an initial dFLC value of less than 50 mg/L a low FLC response is indicated if dFLC < 10 mg/L
SD = NR		Less than a PR	Less than a PR	Less than a PR
PD	From CR, any detectable monoclonal protein	From CR, abnormal FLC ratio (light chain must at least double)	From CR, abnormal FLC ratio (light chain must at least double)	From CR, abnormal FLC ratio (light chain must at least double)

Response Criteria	Serum M Protein/ IFE	Evaluation Mode 1	Evaluation Mode 2	Evaluation Mode 3
	From PR, 50% increase in serum M protein to >0.5g/dL or 50% increase in urine M protein to >200 mg/dL	From PR, Serum FLC increase of ≥ 50% to iFLC > 100 mg/L	From PR, Serum FLC increase of ≥ 50% to dFLC > 50 mg/L	From PR, Serum FLC increase of ≥ 50% to dFLC > 50 mg/L

* Several Case Report Forms include Complete Response as aCR (amyloid Complete Response). There is no distinction between aCR and CR

N Latex FLC versus Clinical Status

For each evaluation mode, the performance of N Latex FLC as an aid in monitoring of AL patient was evaluated by comparing the clinical status assessed by physician (taking into account all available clinical and laboratory information) with the response criteria derived from N Latex FLC based on changes between the initial sample draw and each consecutive blood draw independently. The results are summarized in the following tables. The 95% confidence intervals (CI) were calcuated by bootstrap method to account for the correlations of multiple samples within each subject.

Evaluation Mode 1:

Response Criteria with N Latex FLC	Clinical Status					
	Complete Response	VGPR	Partial Response	Stable Disease	Progressive Disease	Total
CR	19	8	10	6	1	**44**
VGPR	15	40	11	8	1	**75**
PR	0	4	15	6	1	**26**
SD	0	4	17	35	5	**61**
PD	0	0	3	4	9	**16**
Total	**34**	**56**	**56**	**59**	**17**	**222**
Concordance (n/N) (95% CI*)	55.9% (19/34) (28.6;75.7%)	71.4% (40/56) (56.6%;88.9%)	26.8% (15/56) (7.8%;30.2%)	59.3% (35/59) (39.6%;75.0%)	52.9% (9/17) (28.6%; 78.9%)	**53.2% (118/222)**

*****95% CI was calcuated by bootstrap method

Clinical sensitivity and specificity using dichotomized progressive disease (PD)/non-progressive disease results are summarized in the following table:

Evaluation Mode 1		Disease Status		Total
		Progression	No-Progression	
	PD	9	7	16
	No-PD	8	198	206

Response with N Latex FLC	**Total**	17	205	222
Clinical Sensitivity (95% CI*): 52.9% (9/17) (95% CI: 28.6–78.9%) Clinical Specificity (95% CI*): 96.6% (198/205) (95% CI: 95.2–99.5%)				

*95% CI was calcuated by bootstrap method

Evaluation Mode 2:

Response Criteria with N Latex FLC	**Clinical Status**					
	Complete Response	**VGPR**	**Partial Response**	**Stable Disease**	**Progressive Disease**	**Total**
CR	18	8	10	6	1	**43**
VGPR	16	40	11	8	1	**76**
PR	0	4	15	6	0	**25**
SD	0	4	17	34	3	**58**
PD	0	0	3	5	12	**20**
Total	**34**	**56**	**56**	**59**	**17**	**222**
Concordance (n/N) (95% CI*)	52.9% (18/34) (25.0%;74.3%)	71.4% (40/56) (56.6%;88.9%)	26.8% (15/56) (8.0%;30.3%)	57.6% (34/59) (38.2%;72.9.%)	70.6% (12/17) (47.1%; 88.2%)	**53.2% (118/222)**

*95% CI was calcuated by bootstrap method

Clinical sensitivity and specificity using dichotomized progressive disease (PD)/non-progressive disease results are summarized in the following table:

Evaluation Mode 2		**Disease Status**		**Total**
		Progression	**No-Progression**	
Response with N Latex FLC	**PD**	12	8	20
	No-PD	5	197	202
	Total	17	205	222
Clinical Sensitivity (95% CI*): 70.6% (12/17) (95% CI: 47.1–88.2%) Clinical Specificity (95% CI*): 96.1% (197/205) (95% CI: 94.8–99.0%)				

*95% CI was calcuated by bootstrap method

Evaluation Mode 3:

Response Criteria with N Latex FLC	Clinical Status					
	Complete Response	VGPR	Partial Response	Stable Disease	Progressive Disease	Total
CR	18	8	10	6	1	**43**
VGPR	16	40	10	7	1	**74**
PR	0	4	15	6	0	**25**
SD	0	4	18	34	2	**58**
PD	0	0	3	6	13	**22**
Total	**34**	**56**	**56**	**59**	**17**	**222**
Concordance (n/N) (95% CI*)	52.9% (18/34) (24.0;74.2%)	71.4% (40/56) (56.4%;89.1%)	26.8% (15/56) (7.9%;30.3%)	57.6% (34/59) (37.5%;72.3%	76.5% (13/17) (52.9%;93.8%)	**53.2% (118/222)**

*95% CI was calcuated by bootstrap method

Clinical sensitivity and specificity using dichotomized progressive disease (PD)/non-progressive disease results are summarized in the following table:

Evaluation Mode 3		Disease Status		Total
		Progression	No-Progression	
Response with N Latex FLC	**PD**	13	9	22
	No-PD	4	196	200
	Total	17	205	222
Clinical Sensitivity (95% CI): 76.5 (13/17) (95% CI: 52.9; 93.8%) Clinical Specificity (95% CI): 95.6% (196/205) (95% CI: 93.3; 99.0%)				

*95% CI was calcuated by bootstrap method

N Latex FLC versus Freelite Kappa Free and Lambda Free (Predicate)

The clinical performance of N Latex FLC assay as an aid in monitoring of AL patients was compared to the predicate device using the three above evaluation modes. The results are summarized in the following table. The 95% confidence intervals (CI) were calcuated by bootstrap method to account for the correlations of multiple samples within each subject.

Evaluation Mode	N Latex FLC		Freelite Kappa and Lambda Free	
	Sensitivity (n/N) (95% CI*)	Specificity (n/N) (95% CI*)	Sensitivity (n/N) (95% CI*)	Specificity (n/N) (95% CI*)
1	52.9% (9/17) (28.6%; 78.9%)	96.6% (198/205) (95.2%; 99.5%)	64.7% (11/17) (38.9%; 82.4%)	97.6% (200/205) (94.8%; 99.5%)
2	70.6% (12/17) (47.1%; 88.2%)	96.1% (197/205) (94.8%; 99.0%)	58.8% (10/17) (28.6%; 80.0%)	96.6% (198/205) (94.2%; 99.5%)
3	76.5% (13/17) (52.9%; 93.8%)	95.6% (196/205) (93.3%; 99.0%)	64.7% (11/17) (38.9%; 83.3%)	95.6% (196/205) (93.4%; 99.0%)

*95% CI was calcuated by bootstrap method

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.