510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K212379

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 the Atellica CH Analyzer to be used with the previously cleared assay for the intended use as an aid in the evaluation of Monoclonal Gammopathy of Undetermined Significance (MGUS)

B Measurand:

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

C Type of Test:

Turbidimetry; 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 and Atellica CH Analyzer.

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.

Precautions

- 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 (e.g. chronic kidney disease) 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:

Atellica CH Analyzer (K151767)
BN II System (K943997)
BN ProSpec (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, K193047, and K201496. 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 with preservative.
- N FLC Supplementary Reagents A and B: N FLC Supplementary Reagent A contains mouse immunoglobulin in buffered solution with preservative, and N FLC Supplementary Reagent B consists of a buffered salt solution containing detergent with preservative.
- 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:

The N Latex FLC kappa and N Latex FLC lambda assays on the Atellica CH Analyzer are based upon the principles of particle-enhanced turbidimetry. Polystyrene particles coated with antibodies to human free light chains, type kappa or lambda, respectively, are agglutinated when mixed with samples containing free light chain. Monitoring the agglutination by measuring the increase in turbidity, a concentration curve is obtained. The actual change in absorbance 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):

N Latex FLC kappa
N Latex FLC lambda

B Predicate 510(k) Number(s):

K193047

C Comparison with Predicate(s):

Device & Predicate Device(s):	K212379 (Device)	K193047 (Predicate)
Device Trade Name	N Latex FLC Kappa N Latex FLC Lambda	Same
General Device Characteristic Similarities		
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 and Atellica CH Analyzer. Results of FLC measurements should always be interpreted in conjunction with other laboratory and clinical findings.	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.
Sample Type	Serum and EDTA Plasma	Same
Reagent Packaging	3 x 1 mL	Same
Units	mg/L	Same
Measurement	Quantitative	Same
Detection Antibody	Monoclonal mouse anti-human FLC kappa	Same

	Monoclonal mouse anti-antibody FLC lambda	
Reagent Composition	Polystyrene particles coated with monoclonal antibodies	Same
Traceability	Internal reference pool	Same
Calibrator	One level	Same
Calibration Level	42 days	Same
Reference Interval	Kappa: 8.24 – 28.90 mg/L Lambda: 9.10 – 32.60 mg/L Ratio: 0.53 – 1.51	Same
General Device Characteristic Differences		
Analyzer	Evaluation of MGUS on Atellica CH analyzer and BN system	Evaluation of MGUS on BN system
Reagent Handling	Reagent poured into reagent Containers	Bottles placed directly on system
Detection Method	Turbidimetry	Nephelometry
Analytical Measuring Range	On Atellica CH analyzer: Kappa: 3.91 – 60 mg/L Lambda: 5.47 – 70 mg/L (Independent of calibrator lot value)	On BN system: Kappa: 3.4 – 110 mg/L Lambda: 1.9 – 60 mg/L (Calibrator lot value dependent)

VI Standards/Guidance Documents Referenced:

CLSI EP09c: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

See K171742 for precision/reproducibility of the N Latex FLC kappa and lambda assays on BN systems.

The precision of the N Latex FLC kappa and N Latex FLC lambda assays on Atellica CH analyzer were evaluated according to CLSI EP5-A3. Five serum samples (S1, S2, S3, S4 and S5), two EDTA plasma samples (P1 and P2) and two assay specific controls (C1 and C2) covering the analytical measuring range (AMR) were included in this study. The study (N=80) was performed over 20 days with two runs per day and two replicates per run with three reagent lots, three standard lots and three control lots using one Atellica CH analyzer. The results of mean and % Coefficient of Variation (%CV) are summarized below.

Sample	N Latex FLC Kappa			N Latex FLC Lambda		
	Mean (mg/L)	Repeatability %CV	Within-Lab % CV	Mean (mg/L)	Repeatability %CV	Within-Lab % CV
S1	7.82	1.02	1.72	8.04	2.27	3.63
S2	26.61	0.68	1.33	32.89	1.12	3.22
S3	7.72	1.10	1.92	11.30	1.44	4.35
S4	19.08	0.67	1.53	20.94	1.16	4.20
S5	50.08	0.72	1.41	60.94	1.72	4.10
P1	7.62	1.16	1.69	9.22	2.07	3.85
P2	53.84	0.96	2.04	60.07	1.63	3.94
C1	12.14	1.04	1.48	12.00	2.27	4.12
C2	32.07	0.79	1.14	35.09	1.33	3.45

2. Linearity:

See K171742 for linearity of the N Latex FLC kappa and lambda assays on BN systems.

A linearity study was conducted according to CLSI EP06-A to determine the linear AMR of N Latex FLC kappa and N Latex FLC lambda assay on the Atellica CH Analyzer. At least nine different dilutions covering the entire AMR were prepared and measured in at least four replicates using one reagent lot, one standard lot and one control lot. For each sample concentration, the arithmetic mean, standard deviation, and the deviation between the linear regression model and the best fitting polynomial regression model was calculated. The results support the AMR claimed for N Latex FLC kappa and N Latex FLC lambda on the Atellica CH Analyzer: 3.91 to 60.00 mg/L for N Latex FLC kappa; 5.47 to 70.00 mg/L for N Latex FLC lambda.

Hook effect:

See K171742 for high dose hook effect of the N Latex FLC kappa and lambda assays on BN systems.

The hook effect of the N Latex FLC Kappa and N Latex FLC Lambda assays on the Atellica CH Analyzer was evaluated. No high dose hook effect was observed up to an analyte concentration of 30000 mg/L for both assays.

3. Analytical Specificity/Interference:

See K171742 for interference of the N Latex FLC kappa and lambda assays on BN systems.

The N Latex FLC kappa and N Latex FLC lambda assays were evaluated for interference on the Atellica CH Analyzer according to CLSI Guideline EP07-A2 . For each assay, no interference was observed up to the indicated concentration for the tested endogenous substances shown in the following table

	N Latex FLC Kappa	N Latex FLC Lambda
Interferant	**Concentration**	**Concentration**
Hemoglobin	1100 mg/dL	820 mg/dL
Bilirubin (Unconjugated)	65 mg/dL	65 mg/dL
Bilirubin (Conjugated)	65 mg/dL	65 mg/dL
Triglycerides	1115 mg/dL	734 mg/dL
Total Protein	120 g/L	120 g/L
Rheumatoid Factor	888 IU/mL	798 IU/mL

4. Assay Reportable Range:

   The analytical measuring range (AMR) for N Latex FLC kappa and N Latex FLC lambda on the Atellica CH Analyzer is: 3.91 to 60.00 mg/L for N Latex FLC kappa and 5.47 to 70.00 for N Latex FLC lambda.

   If samples are above the AMR, the system automatically dilutes the initial sample aliquot 1:10 allowing to extend the measuring range up to 600.00 mg/L for N Latex FLC kappa and 700.00 mg/L for N Latex FLC lambda.

   If samples are below the AMR, the samples can be re-measured automatically in a 1:1.5 dilution. However, it must be noted that values reported below the AMR are not fully validated.

5. Detection Limit:

   See K171742 for detection limit on BN system

   The same studies were performed on Atellica CH analyzer. The following results are provided in Alliance Application sheet for Atellica analyzer:

   a. Limit of Blank (LoB)
      All results measured on blank samples for the LoB study yielded results below the respective LoQ of each assay.

   b. Limit of Detection (LoD)
      LoD is greater than LoB and equal or below LoQ.

   c. Limit of Quantitation (LoQ)
      LoQ for N Latex FLC kappa and N Latex FLC lambda was determined on the Atellica CH Analyzer according to CLSI guideline EP17-A2. The LoQ is the lowest concentration of analyte with the total error below 19.10% and shown as follows:

      N Latex FLC kappa: 1.037 mg/L
      N Latex FLC lambda: 1.661 mg/L

B Comparison Studies:

1. Method Comparison with Predicate Device:

To demonstrate the equivalent performance of the N Latex FLC kappa and lambda assays on the BN system and Atellica CH analyzer as an aid in evaluation of MGUS, the method comparison study was conducted internally at the Siemens Healthcare Diagnostics Products GmbH site in Marburg, Germany according to CLSI EP09c. Samples derived from MGUS patients (38 for kappa and 35 for lambda) were tested using N Latex FLC kappa and N Latex FLC lambda assays on the Atellica CH Analyzer and the BN ProSpec System. Passing-Bablok regression analysis was performed for each assay and the results are shown in the following table:

	N	Sample Range (mg/L)	Slope (95% CI)	Y-Intercept (95% CI)	Correlation Coefficient
N Latex FLC Kappa	38	6.61–345	0.97 (0.93–1.00)	0.645 (-0.21–1.19)	0.977
N Latex FLC Lambda	35	8.52–181	0.84 (0.75–0.93)	0.123 (-1.69–2.69)	0.970

As the slope of method comparison for FLC lambda on the Atellica CH Analyzer and the BN system is 0.84, the bias was analyzed for the samples around the lower and higher reference interval. The results are shown in the table below:

	Lower Limit of Reference Interval (mg/L)	Predicted Bias (%)	Upper Limit of Reference Interval (mg/L)	Predicted Bias (%)
N Latex FLC Lambda	9.10	-15.7	32.6	-16.9

Because of the observed difference of the result of N Latex FLC lambda on the Atellica CH analyze and BN system, when this assay is used to evaluate the MGUS patients, a warning statement "*The values of FLC kappa or FLC lambda on BN systems and on Atellica® CH Analyzer should not be used interchangeably*" is included in the package insert.

Additionally, to mitigate the exceptionally high negative bias observed for FLC lambda determination when tested on the Atellica CH analyzer, the following limitation is added in the Alliance Application sheet for the assays used on the Atellica CH Analyzer:

"There was >15% negative bias observed for FLC Lambda on Atellica CH analyzer when comparing with BN system for evaluation of MGUS samples. For Non-IgM MGUS and IgM MGUS, physician should consider results of FLC kappa and lambda test as ancillary and make diagnosis based on the totality of the data".

C Clinical Studies:

See K193047 for the clinical studies conducted for evaluation of MGUS using the BN system.

D 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

Each laboratory should determine its own reference intervals since values may vary depending on the individual population studied and for each separate analyzer.

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.