510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K182098

B. Purpose for Submission:

Modification of previously cleared devices – addition of intended use as aid in monitoring of multiple myeloma

C. Measurand:

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

D. Type of Test:

Nephelometry, quantitative

E. Applicant:

Siemens Healthcare Diagnostics Products GmbH

F. Proprietary and Established Names:

N Latex FLC kappa assay
N Latex FLC lambda assay

G. Regulatory Information:

1. Regulation 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 uses:

   N Latex FLC kappa and N Latex FLC lambda assays

   In-vitro diagnostic reagents for the quantitative determination of free light chains (FLC), type kappa or type lambda in human serum and EDTA-plasma by means of particle-enhanced immunonephelometry using the BN Systems. FLC measurements are used as an aid in the diagnosis and monitoring of multiple myeloma (MM) and as an aid in the diagnosis of amyloidosis (AL) in conjunction with other laboratory and clinical findings.

   The response category assignment of Complete Response for the monitoring of MM, is reliant upon the combination of clinical history and other tests including protein electrophoresis, immunofixation and bone marrow, imaging and urine assessments.

2. Indications for use:

   Same as Intended Use

3. Special conditions for use statements:

   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 assay used. Values obtained with different assay methods cannot 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.

4. Special instrument requirements:

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

I. Device Description:

The N Latex FLC kappa and N Latex FLC lambda assays are comprised of the following reagents in liquid form:

N latex FLC reagents: suspension of polysterene particles coated with mouse monoclonal antibodies to either human FLC Kappa or human FLC Lambda with preservative.

N FLC supplementary reagents: mouse immunoglobulin in buffered solution with preservatives.

N FLC standard SL and N FLC controls SL1 and SL2: human free light chains proteins, human serum albumin and protease inhibitors.

J. Substantial Equivalence Information:

1. Predicate device names and 510(k) numbers:

   The Binding Site Freelite® Human Kappa Free Kit and Freelite® Human Lambda Free Kit for use on the Siemens BN™ II - K031016

2. Comparison with predicate:

Similarities		
Item	Device N Latex FLC kappa N Latex FLC lambda	Predicate Freelite® Human Kappa Free and Freelite® Human Lambda Free kits on the Siemens BN™II
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 of measure	mg/L	Same

Differences		
Item	Device	Predicate
Indication for use	In-vitro diagnostic reagents for the quantitative determination of free light chains (FLC), type kappa or type lambda in human serum and EDTA-plasma by means of particle- enhanced immunonephelometry using the BN Systems. FLC measurements are used as an aid in the diagnosis and monitoring of multiple myeloma (MM) and as an aid in the diagnosis of amyloidosis (AL) in conjunction with other laboratory and clinical findings. The response category assignment of 'Complete Response' for the monitoring of MM, is reliant upon	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.

Differences		
Item	Device	Predicate
	the combination of clinical history and other tests including protein electrophoresis, immunofixation and bone marrow, imaging and urine assessments.	
Sample type	Serum and EDTA plasma	Serum and urine
Detection antibody	Kappa: Monoclonal mouse anti-human FLC kappa antibody coated onto polysterene particles Lambda: Monoclonal mouse anti-human FLC lambda antibody coated onto polysterene 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
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 to 19.40 mg/L Lambda: 5.71 to 26.30 mg/L Ratio: 0.26 – 1.65

K. Standard/Guidance Document Referenced (if applicable):

L. Test Principle:

The FLC test systems are based upon the principles of particle-enhanced immunonephelometry. Polystyrene particles coated with monoclonal antibodies to human free light chains (FLCs), type kappa or lambda, are agglutinated when mixed with samples containing FLCs. 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.

M. Performance Characteristics:

1. Analytical performance:

a. Precision/Reproducibility:

See K171742

b. Linearity/assay reportable range:

See K171742

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

See K171742

d. *Detection limit:*

See K171742

e. *Analytical specificity:*

See K171742

f. *Assay cut-off:*

See expected values/reference range below.

2. Comparison studies:

a. *Method comparison with predicate device:*

See K171742

b. *Matrix comparison:*

See K171742

3. Clinical studies:

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 multiple myeloma (MM) and light chain multiple myeloma (LCMM) subjects was determined from a retrospective clincal study. Changes in FLC Kappa and FLC Lambda levels in serial serum samples from subjects diagnosed with MM and LCMM during treatment were compared to clinical response categories based on International Myeloma Working Group (IMWG) as determined by the clinicians.

The patient inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Confirmed diagnosis of MM or LCMM
- At least four blood collections in intervals of ≥ three weeks
- Informed consent available
- Clinical information of response level available

Exclusion criteria:

- Less than four blood collections
- No informed consent available
- Patients subsequently diagnosed with another disease

A total of 125 (104 MM and 21 LCMM) subjects were enrolled in the study. Among them, 27 subjects were excluded: 17 subjects had less than four sample draws; four MM subjects were re-diagnosed to Waldenstrom Macroglobulinemia; two subjects had no informed consent available; and four subjects had no available clinical information about response level. Therefore, a total 98 subjects (81 IgG, IgA and IgM MM and 17 Kappa and Lambda LCMM subjects) with a total of 391 serum samples were used in the study analysis.

Of the 98 subjects, 47 (47%) were male and 51 (52%) were female. The mean age was 65 years and the range was 35 to 92 years. The majority of subjects (n=70, 71%,) were Caucasian, the remaining subjects included 18 (18%) African American, one (1%) Asian and nine (9%) Unknown.

A total of 391 draws were collected from 98 subjects. The mean number of draws per subject was five, ranging from four to seven draws. The duration of the monitoring days ranged from 88 days to 1338 days.

The information collected for each sample included the following: (a) general information including patient's demographic information and date of blood sample drawn; (b) clinical information including patient's diagnosis report/medical notes, treatment initiated, and diagnostic response criteria; c) laboratory data including serum electrophoresis results, serum/ urine immunofixation electrophoresis, serum FLC Kappa and FLC Lambda, CRAB (Calcium, Renal Failure, Anemia, Bone lesions) status, and plasma cell count.

Results:

The performance of the N Latex FLC kappa and N Latex FLC lambda assays as aid in monitoring MM was evaluated by testing a total of 391 samples from 98 subjects consisting of 98 baseline values and 293 monitoring observations and comparing to clinical disease response status.

At each follow-up visit, the percentage change of the Involved FLC Kappa (iFLC Kappa) or Involved FLC Lambda (iFLC Lambda) was calculated by comparing the test result to the test result from the previous visit. The monitoring response criteria based on the FLC results were based on the FLC ratio, % relative change of difference between both FLC (rd_FLC), M protein level and IFE monocloncal protein detection.

The clinical assessment for each monitoring observation was provided by the attending physician who was responsible for the corresponding therapy decisions based on therapy response criteria defined according to International Myeloma Working Group (IMWG) 2011/National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Multiple Myeloma. Clinical status of each monitoring event was

categorized into one of six response categories: Stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD).

Data were analyzed based on the comparison of disease category determined from N Latex assays to clinical assessement.

Results of N Latex FLC kappa and N Latex FLC lambda assays in combination with other laboratory results were used to assign a response category and compared to the clinical assessment according to the table below:

Response Category	**Response Criteria based on N Latex FLC, SPE, IFE Results**	**Clinical Assessment based on IMWG**
Good Response	FLC ratio normal, M protein not detectable and IFE negative*	sCR
		CR
Moderate Response	≥ 50 to ≥ 90% reduction of rd_dFLC** and ≥ 50 to ≥ 90% reduction of M protein	VGPR
		PR
Stable Disease	50% reduction to 25% increase of rd_dFLC and 50% reduction to 25% increase of M protein	SD
Progressive Disease	≥ 25% increase of rd_dFLC and ≥ 25% increase of M protein AND increase of d_dFLC*** ≥ 100 mg/L and increase of M protein ≥ 0.5 g/L	PD

*Applies only to MM population
**rd_dFLC = (dFLC t2 – dFLC t1)/ dFLC t1
***d_dFLC = dFLC t2 – dFLC t1 (with 'dFLC = iFLC – ni FLC')

Definitions:

- t1 = time point 1; t2 = time point 2
- rd = relative difference
- iFLC = involved FLC; niFLC = not involved FLC
- Relative change of involved FLC: rd_iFLC = (iFLC t2 – iFLC t1)/ iFLC t1
- Relative change of difference between both FLC: dFLC = iFLC – niFLC

The performance of N Latex FLC Kappa and FLC Lambda in combination with other laboratory tests compared to the clinical assessment is summarized in the following table:

Response Category	Clinical Assessment				
	Good Response	Moderate Response	Stable Disease	Progressive Disease	Total
Good Response	21	3	6	1	31

Moderate Response	10	104	38	16	168
Stable Disease	3	24	126	18	171
Progressive Disease	0	0	9	12	21
Total	34	131	179	47	391
Agreement	62%	79%	70%	26%	67%

Discordance results:

The response criteria established by clinicians are often based on multiple factors besides FLC results, therefore FLC results alone might lead to a different classification.

The clinical disease reponse categories were condensed into two clinical status categories: "Progression" and "No-progression". Subjects with 'Progression' consist of those monitoring events defined as 'Progressive Disease'. Subjects with 'No-Progression' consist those monitoring events defined as 'Good Response, Moderate Response, and Stable Disease Response' categories. The performance N-Latex FLC results compared to the clinical status are summarized as follows:

		Clinical Status		
		Progression	No Progression	Total
Change in N Latex FLC	Positive*	12	9	21
	Negative**	35	335	370
	Total	47	344	391
Clinical Sensitivity: 26% (12/47) (95% CI: 13.9% – 40.3%) Clinical Specificity: 97% (335/344) (95% CI: 95.1%– 98.8%)				

*Positive: ≥25% rd_dFLC and d_dFLC ≥100 mg/L
**Negative: <25% rd_dFLC and d_dFLC FLC <100 mg/L

b. Other clinical supportive data (when a. and b. are not applicable):

The performance of N Latex FLC kappa and FLC lambda assays were also compared to the predicate device based on the disease response categories described above.

In this retrospective clinical study, all samples were tested with the N Latex FLC kappa and FLC lambda assays and with the predicate device. The perfomance of N Latex FLC kappa and N Latex FLC lambda assays compared to the predicate device based on the same disease response category is summarized as follows:

Response based on N Latex FLC results	Response Based on Freelite Results				
	Good Response	Moderate Response	Stable Disease	Progressive Disease	Total
Good Response	27	2	0	1	31
Moderate Response	0	66	15	0	81
Stable Disease	0	13	238	7	258
Progressive Disease	0	0	5	16	21
Total	**27**	**81**	**259**	**24**	**391**
Agreement	**100%**	**81%**	**92%**	**67%**	**89%**

4. Clinical cut-off**:**

   Not applicable

5. Expected values/Reference range:

   See K171742

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

O. Conclusion:

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