

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

K160819

B. Purpose for Submission:

New instrument for a cleared IVD assay

C. Measurand:

Immunoglobulin IgA Kappa (combined α heavy and κ light chain) and Immunoglobulin IgA Lambda (combined α heavy and λ light chain)

D. Type of Test:

Quantitative, Turbidimetry

E. Applicant:

The Binding Site Group, Ltd.

F. Proprietary and Established Names:

Optilite Hevylite[®] Human IgA Kappa Kit and Optilite Hevylite[®] Human IgA Lambda Kit

G. Regulatory Information:

1. Regulation section:

21 CFR §866.5510, Immunoglobulins A, G, M, D, and E Immunological Test System

2. Classification:

Class II

3. Product code:

OPX - IgA Kappa (Heavy and Light chain Combined). Antigen, antiserum, control

OPY - IgA Lambda (Heavy and Light chain Combined). Antigen, antiserum, control

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

The Optilite Hevylite Human IgA Kappa is a quantitative *in vitro* assay intended for the measurement of IgA Kappa (IgA heavy chain and Kappa light chain intact immunoglobulin) in serum using the Binding Site Optilite analyser. Measurement of Hevylite Human IgA Kappa is used alongside Hevylite Human IgA Lambda to calculate the IgA Kappa/IgA Lambda ratio. The Hevylite Human IgA Kappa/IgA Lambda ratio can be used when monitoring previously diagnosed IgA multiple myeloma and is used in conjunction with other laboratory tests and clinical evaluations. The assignment of complete response is reliant upon other tests including immunofixation, bone marrow and urine assessments.

The Optilite Hevylite Human IgA Lambda is a quantitative *in vitro* assay intended for the measurement of IgA Lambda (IgA heavy chain and Lambda light chain intact immunoglobulin) in serum using the Binding Site Optilite analyser. Measurement of Hevylite Human IgA Lambda is used alongside Hevylite Human IgA Kappa to calculate the IgA Kappa/IgA Lambda ratio. The Hevylite Human IgA Kappa/IgA Lambda ratio can be used when monitoring previously diagnosed IgA multiple myeloma and is used in conjunction with other laboratory tests and clinical evaluations. The assignment of complete response is reliant upon other tests including immunofixation, bone marrow and urine assessments.

2. Indication(s) for use:

Same as intended use.

3. Special conditions for use statement(s):

For prescription use only.

Warning: The result of Hevylite Human IgA Kappa in a given specimen determined with assays with different manufacturers and different instrument platforms 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 Hevylite Human IgA Kappa 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 Hevylite IgA Kappa 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.

Warning: The result of Hevylite Human IgA Lambda in a given specimen determined with assays with different manufacturers and different instrument platforms 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 Hevylite Human IgA Lambda 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 Hevylite Human IgA 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:

The Binding Site Optilite Analyzer

I. Device Description:

The Optilite Hevylite Human IgA Kappa Antiserum and Optilite Hevylite Human IgA Lambda Antiserum contain vials of ready-to-use polyclonal monospecific sheep anti-IgA antisera against combined α heavy and κ light chain or combined α heavy and λ light chain, one level calibrator, controls (low and high) and Optilite Diluent 2 in liquid form. The reagents contain 0.099% sodium azide, 0.1% E-amino-n-caproic acid (EACA), 1mM ethylenediaminetetraacetic acid (EDTA) and 0.01% benzamidine as preservatives.

J. Substantial Equivalence Information:

1. Predicate device names and predicate 510(k) number:

Hevylite™ Human IgA Kappa Kit and Hevylite™ Human IgA Lambda Kit for use on Siemens BN™ II Systems (K140105)

2. Comparison with predicate:

Similarities		
Item	Device Optilite Hevylite® IgA Kappa (IgA κ) and IgA Lambda (IgA λ) Kits	Predicate Hevylite™ IgA Kappa (IgA κ) and IgA Lambda (IgA λ) Kits on Siemens BN™ II
Intended Use	Quantitative in vitro assay for the measurement of IgA Kappa (IgA heavy chain and Kappa light chain intact immunoglobulin) and IgA Lambda (IgA heavy chain and Lambda light chain intact immunoglobulin) in serum.	Same

Similarities		
Item	Device Optilite Hevylite [®] IgA Kappa (IgAκ) and IgA Lambda (IgAλ) Kits	Predicate Hevylite [™] IgA Kappa (IgAκ) and IgA Lambda (IgAλ) Kits on Siemens BN [™] II
	Measurement of Hevylite Human IgA Kappa is used alongside Hevylite Human IgA Lambda to calculate the IgA Kappa/IgA Lambda ratio. The Hevylite Human IgA kappa/IgA lambda ratio can be used when monitoring previously diagnosed IgA multiple myeloma and is used in conjunction with other laboratory tests and clinical evaluations. The assignment of complete response is reliant upon other tests including immunofixation, bone marrow and urine assessments.	
Method	Nephelometry/ Turbidimetry	Same
Analyte	IgA Kappa and IgA Lambda	Same
Antibody	Polyclonal monospecific Sheep anti-human combined α heavy and κ light chain or combined α heavy and λ light chain	Same
Control	Binding Site High and Low Control	Same
Calibrator	Single level Binding Site Hevylite Calibrator auto-diluted to six different concentrations	Same
Traceability	ERM–DA470k	Same
Sample Matrix	Serum	Same
Capture antibody	Sheep anti-human IgA combined	Same

Differences		
Item	Device Optilite Hevylite [®] IgA Kappa (IgAκ) and IgA Lambda (IgAλ) Kits	Predicate Hevylite [™] IgA Kappa (IgAκ) and IgA Lambda (IgAλ) Kits on Siemens BN [™] II
Instrument	Binding Site Optilite	Siemens BN [™] II Systems
Method	Turbidimetry	Nephelometry
On-board stability	11 days	Not stated
Measuring Range	At standard 1 + 9 dilution:	At standard 1/100 dilution:

Differences		
Item	Device Optilite Hevylite® IgA Kappa (IgAκ) and IgA Lambda (IgAλ) Kits	Predicate Hevylite™ IgA Kappa (IgAκ) and IgA Lambda (IgAλ) Kits on Siemens BN™ II
	IgAκ: 0.18–11.2 g/L IgAλ: 0.16–10.4 g/L Extended Range for IgAκ: 1+ 0 dilution: 0.018–1.12 g/L 1+ 59 dilution: 1.08–67.2 g/L 1+ 99 dilution: 1.8–112 g/L Extended Range for IgAλ: 1+ 0 dilution: 0.016–1.04 g/L 1+ 59 dilution: 0.96–62.4 g/L 1+ 99 dilution: 1.6–104 g/L	IgAκ: 0.35–11.2 g/L IgAλ: 0.33–10.4 g/L Extended Range for IgAκ: 1/5 dilution: 0.018–0.56 g/L 1/20 dilution: 0.07–2.24 g/L 1/400 dilution: 1.40–44.8 g/L 1/2000 dilution: 7.0–224 g/L Extended Range for IgAλ: 1/5 dilution: 0.016–0.520 g/L 1/20 dilution: 0.065–2.08 g/L 1/400 dilution: 1.40–41.6 g/L 1/2000 dilution: 6.5–208 g/L
Reference Interval	IgAκ: 0.588–2.984 g/L IgAλ: 0.432–2.035 g/L IgAκ/IgAλ Ratio: 0.911–2.416	IgAκ: 0.48–2.82 g/L IgAλ: 0.36–1.98 g/L IgAκ/IgAλ Ratio: 0.80–2.04

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

CLSI EP05-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline–Second Edition

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

CLSI EP07-A2: Interference Testing in Clinical Chemistry

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation

CLSI C28-A3: Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory

L. Test Principle:

The determination of soluble antigen concentration by turbidimetric methods involves the reaction with specific antiserum to form insoluble complexes. When light is passed through the suspension formed a portion of the light is transmitted and focused onto a photodiode by an optical lens system. The amount of transmitted light is indirectly proportional to the specific protein concentration in the test sample. Concentrations are automatically calculated by reference to a calibration curve stored within the instrument.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

All results met the manufacturer's pre-specified acceptance criteria.

a. Precision/Reproducibility:

The study design followed the recommendations of CLSI EP05-A2. The within-run, between-run, between-day, between-lot and between-instrument precision were determined by testing six IgA κ and five IgA λ serum samples over 21 days with two runs per day and two replicates per run on four different reagent lots on six analyzers for IgA κ and three different reagent lots on three analyser for IgA λ . Results are summarized below.

IgA κ Precision studies:

Sample	Mean (g/L)	Within Run		Between Run		Between Day		Between instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.298	0.01	2.1	0.01	3.1	0.02	5.7	0.01	4.3	0.02	6.9
2	0.853	0.01	1.7	0.02	2.2	0.02	2.7	0.01	1.1	0.03	3.9
3	1.650	0.05	2.8	0.04	2.2	0.09	5.4	0.04	2.3	0.11	6.5
4	2.449	0.05	1.9	0.07	2.9	0.09	3.9	0.04	1.5	0.13	5.2
5	3.379	0.11	3.1	0.12	3.4	0.14	4.0	0.08	2.4	0.22	6.1
6	9.115	0.12	1.4	0.15	1.7	0.41	4.5	0.25	2.7	0.45	5.0

IgA λ Precision studies:

Sample	Mean (g/L)	Within Run		Between Run		Between Day		Between instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.301	0.00	1.3	0.01	1.8	0.02	6.5	0.01	3.0	0.02	6.9
2	0.935	0.02	1.7	0.01	1.1	0.04	4.3	0.02	2.4	0.04	4.7
3	1.633	0.04	2.3	0.03	1.8	0.15	9.0	0.08	5.7	0.15	9.5
4	2.317	0.04	1.9	0.06	2.5	0.20	8.7	0.15	6.5	0.21	9.3
5	8.582	0.11	1.3	0.14	1.6	0.26	3.0	0.07	0.8	0.31	3.7

b. Linearity/assay reportable range:

A linearity study was performed following CLSI EP6-A. The linearity of the IgA κ and IgA λ assays have been confirmed using serially diluted serum samples (IgA κ myeloma sample diluted with IgA κ depleted sample and IgA λ elevated polyclonal sample diluted with IgA λ depleted sample) to cover the standard (1 + 9) dilution measuring range 0.18–11.2 g/L and 0.16–10.4 g/L respectively. Deviation from linearity were: $\leq 6.6\%$ and $\leq 4.2\%$ for IgA κ and IgA λ and the weighted linear

regression observed versus % high pool were: $y = 12.91x - 0.26$ and $y = 12.33x + 0.00$, respectively

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

Traceability: An Internal Reference material (IR) was assigned by comparison with the Reference Material DA470K.

Stability: A real-time stability study of unopened kits was performed on three lots of Optilite Hevylite IgA Kappa and Optilite Hevylite IgA Lambda kits with testing time intervals at day 0, 3, 6.5, 10, 13 months. Data support a shelf life claim of 12 months at 2–8° C.

Open-vial stability was performed on three lots of Optilite IgA Kappa and Optilite IgA Lambda kits with testing time intervals at day 0, and 1, 2, and 3 months. Data support the open vial stability claim of 3 months at 2–8° C.

On-board stability was performed on three lots of Optilite IgA Kappa and Optilite IgA Lambda kits with testing time intervals at 0 and 14 days. Data support the on-board stability claim of 14 days, provided that the power is left switched on as stated in the product insert.

All stability results met the manufacturer's pre-specified acceptance criteria.

d. Detection limit:

The analytical sensitivity was determined in accordance with the non-parametric study design in CLSI EP17-A. The Limits of Blank (LoB) were based on 60 determinations of analyte-depleted sample and was estimated at the 95% percentile of the distribution. The Limits of Detection (LoD) were calculated using the formula $LoD = LoB + c\beta SDs$, where $c\beta$ is 1.645 and SD is the combined standard deviation of five low level samples of serum samples diluted with analyte depleted serum to achieve a concentration close to the bottom of the measuring range. The samples were tested twelve times over five days and the total error (0.0588 g/L for IgA κ and 0.0432 g/L for IgA λ) were within the maximum allowable total error. The Limits of Quantitation (LoQ) were calculated from the total error of the LoD study. The tabulated summary is shown below:

	LoB	LoD	LoQ
IgA Kappa	0.000 g/L	0.002 g/L	0.018 g/L
IgA Lambda	0.000 g/L	0.001 g/L	0.016 g/L

e. Analytical specificity:

Interference:

Interferences were assessed according to CLSI EP07-A2 by testing four serum

samples with different IgA Kappa and IgA Lambda concentration ranges: (1) within the reference interval serum samples, IgA κ target level: 1.001 g/L and IgA λ target level: 0.847 g/L; (2) close to the lower medical decision point (MDP) serum samples, target levels: 0.539 g/L and 0.316 g/L respectively; (3) close to the higher MDP serum samples, target levels 2.259 g/L and 2.010 g/L respectively; (4) samples above the MDP), target levels 8.363 g/L and 7.997 g/L respectively. Each sample was spiked with interfering substances and tested in replicate. The manufacturer's acceptance criteria were that the mean results from the spiked samples must be within $\pm 10\%$ of the mean of the control samples.

No significant assay interference effects were observed when the four samples of IgA κ and IgA λ were tested with bilirubin at 200 mg/L, hemoglobin at 5 g/L, triglyceride at 1000 mg/dL or Intralipid at 200 mg/dL and the 15 commonly used drugs at the concentrations given below. However 1000 mg/dL Intralipid showed signs of interference. The Package Insert states: *"Lipemic samples are known to interfere with this assay and therefore should not be analysed using this assay"*. In addition the 'Limitation section' also states that *"Turbidimetric assays are not suitable for measurement of highly lipemic or hemolysed samples"*.

Drug	Concentration tested
Acetaminophen	1324 $\mu\text{mol/L}$
Acetylsalicylic Acid	3.63 mmol/L
Ascorbic Acid	342 $\mu\text{mol/L}$
Bortezomib	6 mg/mL
Caffeine	308 $\mu\text{mol/L}$
Cimitidine	79.2 $\mu\text{mol/mL}$
Cyclophosphamide Monohydrate	60 $\mu\text{g/L}$
Digoxin	7.8 nmol/L
Furosemide	90 $\mu\text{mol/L}$
Ibuprofen	2425 $\mu\text{mol/L}$
Methotrexate	2 mmol
Penicillin	75 mg/L
Phenytoin	198 $\mu\text{mol/L}$
Pomalidomide	100 $\mu\text{g/mL}$
Prednisolone	100 $\mu\text{g/mL}$
Theophylline	222 $\mu\text{mol/L}$

Cross-reactivity studies:

For IgA κ , the possibility of cross reactivity with other immunoglobulin heavy chain/light chain combinations was assessed by assaying eight IgG κ , five IgG λ , nine IgM κ , five IgM λ , six IgA λ , one Free Kappa and one Free Lambda myeloma samples. No significant ($< 4\%$) cross reactivity were observed.

For IgA λ , the possibility of cross reactivity with other immunoglobulin heavy chain/light chain combinations was assessed by assaying eight IgG κ , five IgG λ , seven IgM κ , four IgM λ , six IgA κ , one Free Kappa and one Free Lambda myeloma samples. No significant (< 1%) cross reactivity were observed.

Antigen Excess Detection

The possibility of antigen excess occurring when using the device on The Binding Site SPA_{PLUS} was evaluated with nine monoclonal IgA Kappa and six monoclonal IgA Lambda samples with concentrations above the 0.18–11.2 g/L and 0.16–10.4 g/L standard measuring ranges respectively. No antigen excess effect up to 81.1 g/L of IgA κ and 101.3 g/L of IgA λ concentration levels were observed at 1 + 9 dilution.

f. Assay cut-off:

Refer to Expected values

2. Comparison studies:

a. Method comparison with predicate device:

IgA Kappa:

A comparison study was performed by analysing 259 samples (including 63 IgA Kappa paraprotein and 41 IgA Lambda paraprotein samples, 29 donor samples and 127 other clinical samples, covering the range 0.02–64.4 g/L) using the Optilite IgA Kappa Kit and an alternative commercially available assay. Passing Bablok regression analysis generated the results below.

IgA Lambda:

A comparison study was performed by analysing 217 samples (including 38 IgA Kappa paraprotein and 41 IgA Lambda paraprotein samples, 29 donor samples and 109 other clinical samples, covering the range 0.07–31.8 g/L) using the Optilite IgA Lambda Kit and an alternative commercially available assay.

Passing Bablok regression analysis generated the following results:

Assay	N	Sample Range	Passing & Bablok	Slope 95% CI	Intercept 95% CI
IgA Kappa	259	0.02–64.4 g/L	$y = 1.09x + 0.03$ g/L	1.07 to 1.11	-0.01 to 0.07
IgA Lambda	217	0.07–31.8 g/L	$y = 1.09x - 0.02$ g/L	1.06 to 1.12	-0.04 to -0.01
IgA κ /IgA λ ratio	211	0.001–273.1	$y = 1.01x + 0.09$	0.97 to 1.07	0.04 to 0.14

The following regression equation based on the study above was used for the transformation in the data modeling described below.

	Slope	Intercept
IgA Kappa	1.09	0.03
IgA Lambda	1.09	-0.02

The slope and the intercept were applied to the previous data using the following equation: $(Original\ result \times Slope) + Intercept$

As the intercepts were negative, data that were already close to LoQ are transformed into negative values by the formula; however, negative IgA Kappa and IgA Lambda results are not possible. Therefore, results that were transformed were capped at LoQ (IgA Kappa: 0.018 g/L and IgA Lambda: 0.016 g/L).-Passing Bablok regression equations were generated with the 3000 bootstrapped patient data points with the following results:

Assay	N	Sample Range	Regression Equation	Slope 95% CIs	Intercept 95% Cis
IgA Kappa	2817	0.02 to 64.4 g/L	$1.09 + 0.02$	1.079 to 1.091	0.001 to 0.028
IgA Lambda	2759	0.02 to 47.3 g/L	$1.09 + 0.04$	1.084 to 1.098	0.011 to 0.056
IgA Kappa / IgA Lambda	2803	0.00 to 273.08	$1.01 + 0.10$	0.999 to 1.029	0.079 to 0.111

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity/ clinical specificity:

Not applicable

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

Transformation of the BN II Study onto Optilite Study

Purpose of the study

The purpose of this study was to compare the clinical HLC Response categorization of the predicate and from the Optilite Hevylite IgA Kappa and Optilite Hevylite IgA

Lambda Kit results obtained from samples taken at multiple time points from IgA Kappa and IgA Lambda multiple myeloma patients during the course of their disease. The Sponsor generated Passing and Bablok regression equations for the comparison study of the Optilite kits against the predicate kits. The regression equation was then modelled with the existing 449 monitoring sample results from the original BNII submission to evaluate the clinical validity of the new device.

Table 1: HLC Monitoring Response Category

Complete Response (CR)	HLC ratio within the normal range, negative urine immunofixation (where available) and $\leq 5\%$ plasma cells in bone marrow.
Very Good Partial Response (VGPR)	$> 94\%$ reduction of HLC ratio from baseline and urine M-immunoglobulin level < 100 mg/24hrs.
Partial Response (PR)	Reduction of HLC ratio from baseline between 60–94% and reduction in 24hr urinary M-immunoglobulin by $\geq 90\%$ from baseline or ≤ 200 mg/24hrs.
Stable Disease (SD)	A change in HLC ratio from baseline $< 24\%$ increase but $< 60\%$ reduction
Progressive Disease (PD)	$\geq 24\%$ increase in HLC ratio from baseline (the absolute increase in involved IgA must be ≥ 5 g/L) or $\geq 25\%$ increase in urine M-immunoglobulin from baseline (the absolute increase must be ≥ 200 mg/24hrs).

Optilite HLC Response Category Study

Assignment of classification was based on the HLC Monitoring Response Category detailed in Table 1, using all assay data available. Responses were categorized in accordance with NCCN Guidelines v.1.2011 by using the percentage (%) change in SPEP or total IgA from baseline. Responses were characterized as progressive disease (PD), stable disease (SD), partial response (PR), very good partial response (VGPR) and complete response (CR). Kappa Statistics was used to evaluate the agreement between test and the clinical status as determined by clinical evaluation combined with either the test or predicate device.

Optilite Monitoring Study Design

A comparison study using 33 monitoring samples from 20 patients (10 IgA Kappa and 10 IgA Lambda) was performed to compare the BN II HLC response category assigned to those observed with the Optilite Hevylite IgA Kappa and IgA Lambda Kits. (Note: The Optilite HLC monitoring response categories were based on NCCN v1.2011 Treatment Response Classification category. The Optilite HLC monitoring response category is not to be used interchangeably with other manufacturer's assays or with any other instrument platform monitoring response category.) The results of comparison study using 33 monitoring samples are shown in the table below:

Observed		BN II HLC response					
		CR	VGPR	PR	SD	PD	Total
Optilite HLC Response	CR	0	0	0	0	0	0
	VGPR	0	2	0	0	0	2
	PR	0	0	1	0	0	1

	SD	0	0	1	27	0	28
	PD	0	0	0	1	1	2
	Total	0	2	2	28	1	33
Linear Weighted Kappa (95% CIs)		0.85 (0.63–1.06)					
Kappa (95% CIs)		0.78 (0.63–0.93)					

These monitoring data were also supported by additional statistical regression equation modelling data.

Data Modeling

Data modeling procedure was carried out in the remaining patient samples which were not being included in the Optilite Response Category study. The Passing and Bablok regression equations derived from the previously cleared 449 BN II data set was mathematically transformed using the Optilite regression equation. The statistical regression equation modelling results are summarized in the tables below.

A summary of the Cohen's Kappa results are provided below:

Observed		BN II Assigned HLC* response					
		CR	VGPR	PR	SD	PD	Total
Optilite H/L** transformed data	CR	18	0	0	0	0	18
	VGPR	9	151	3	0	0	164
	PR	1	4	117	8	0	128
	SD	0	0	2	115	1	118
	PD	0	0	0	0	20	21
	Total	28	155	122	123	21	449
Linear Weighted Kappa (95% CIs)		0.94 (95% CIs: 0.92–0.96)					
Unweighted Kappa (95% CIs)		0.92 (95% CIs: 0.90–0.93)					

*HLC: HevyLite Chain Response

**H/L: H: highest kappa; L: lowest lambda; For H/L - applied the imprecision values to generate the highest kappa and the lowest lambda possible.

Observed		BN II Assigned HLC* response					
		CR	VGPR	PR	SD	PD	Total
Optilite L/H*** transformed data	CR	21	0	0	0	0	21
	VGPR	7	152	3	0	0	162
	PR	0	3	117	7	0	127
	SD	0	0	2	116	0	118
	PD	0	0	0	0	21	21

	Total	28	155	122	123	21	449
Linear Weighted Kappa (95% CIs)	0.96 (95% CI: 0.94–0.97)						
Unweighted Kappa (95% CIs)	0.93 (95% CI: 0.92–0.95)						

* HLC: HevyLite Chain Response

***For L/H – applied the imprecision values to generate the lowest kappa and highest lambda results possible.

The HLC Optilite IgA Monitoring Response Category in the two Tables above were derived from the NCCN v1.2011 *Guidelines on Treatment Response Classification* as shown in Table below.

Table: Comparison of Treatment Response Classification–NCCN v1.2011 and HevyLite IgA kappa/lambda ratio (HLC ratio)

Response	NCCN v1.2011	Disease Monitoring Using HLC Optilite IgA
Complete Response (CR)	Negative IFE on the serum and urine and disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow	HLC ratio within the normal range (Optilite IgA κ /IgA λ Ratio 0.911–2.416 and negative urine immunofixation and $\leq 5\%$ plasma cells in bone marrow (where available)
Very Good Partial Response (VGPR)	Serum and urine M protein detectable by IFE but not SPEP or $\geq 90\%$ reduction in serum M protein level plus urine M protein level < 100 mg per 24 hours	> 94% reduction of HLC ratio from baseline and urine M protein level < 100 mg per 24 hours.
Partial Response (PR)	$\geq 50\%$ reduction of serum M protein and reduction in 24 hour urinary M protein by $\geq 90\%$ or to < 200 mg per 24 hours.	Reduction of HLC ratio from baseline between 60–94% and reduction in 24 hour urinary M protein by $\geq 90\%$ or to < 200 mg per 24 hours.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease	A change in HLC ratio from baseline $< 24\%$ increase but $< 60\%$ reduction.

Response	NCCN v1.2011	Disease Monitoring Using HLC Optilite IgA
Progressive Disease (PD)	Increase of $\geq 25\%$ from baseline in 1 or more: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) • Urine M component and/or (the absolute increase must be $\geq 200\text{mg}/24\text{hr}$) • Bone marrow plasma cell percentage: the absolute percentage must be $\geq 10\%$ • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia	$\geq 24\%$ increase in HLC ratio from baseline (the absolute increase in involved IgA must be ≥ 5 g/L) or a $\geq 25\%$ increase in urine M-component from baseline (the absolute increase must be $\geq 200\text{mg}/24\text{hr}$)

4. Clinical cut-off:

Refer to discussion above.

5. Expected values/Reference range:

Reference Adult Serum	Mean	Median	95th Percentile Range
IgA Kappa (g/L)	1.441	1.292	0.588–2.984
IgA Lambda (g/L)	1.013	0.915	0.432–2.035
IgA Kappa/IgA Lambda Ratio	1.451	1.401	0.911–2.416

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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