510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K220001

B Applicant

Diazyme Laboratories Inc.

C Proprietary and Established Names

Diazyme Human Kappa (κ) Free Light Chain Assay
Diazyme Human Lambda (λ) Free Light Chain Assay

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

B Measurand:

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

C Type of Test:

Latex particle enhanced immunoturbidimetric, quantitative

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Diazyme Human Kappa Free Light Chain Assay is intended as a latex particle enhanced immunoturbidimetric assay for the quantitative determination of Kappa Free Light Chain (FLC) concentration in serum on validated analyzers. The measurement of Kappa FLC in conjunction with Lambda FLC aids in the diagnosis and monitoring of multiple myeloma in conjunction with other laboratory and clinical findings. For in-vitro diagnostic use only.

The Diazyme Human Lambda Free Light Chain Assay is intended as a latex particle enhanced immunoturbidimetric assay for the quantitative determination of Lambda Free Light Chain (FLC) concentration in serum on validated analyzers. The measurement of Lambda FLC in conjunction with Kappa FLC aids in the diagnosis and monitoring of multiple myeloma in conjunction with other laboratory and clinical findings. For in-vitro diagnostic use only.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Warning: The result of the Kappa FLC or Lambda FLC 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 Kappa FLC or Lambda FLC 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 Kappa FLC and Lambda FLC 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.

D Special Instrument Requirements:

Roche cobas c501 analyzer

IV Device/System Characteristics:

A Device Description:

The Diazyme Human Kappa (κ) Free Light Chain Assay is comprised of the following reagents:

- Reagent R1: Tris buffer solution

- Reagent R2: Latex particles coated with polyclonal rabbit and goat anti-human kappa FLC antibodies

Material required but not provided

- Calibrators: A five-level set in liquid form (5 x 1 mL) with target concentrations: 10, 20, 40, 80, 160 mg/L, ready to use
- Controls Set: Two levels (15 mg/L and 30 mg/L), serum based, liquid form

The Diazyme Human Lambda (λ) Free Light Chain Assay is comprised of the following reagents:

- Reagent R1: Tris buffer solution
- Reagent R2: Latex particles coated with polyclonal rabbit anti-human lambda FLC antibodies

Material required but not provided

- Calibrators: A five-level set in liquid form (5 x 1 mL) with target concentrations: 10, 25, 55, 110, 220 mg/L, ready to use
- Control Set: Two levels (15 mg/L and 30 mg/L), serum based, liquid form

B Principle of Operation:

The Diazyme Human Kappa (κ) Free Light Chain Assay or the Diazyme Human Lambda (λ) Free Light Chain Assay is based on a latex enhanced immunoturbidimetric assay. Kappa FLC or Lambda FLC in the sample binds to specific anti-Kappa FLC or anti-Lambda FLC antibody, which is coated on latex particles, and causes agglutination. The degree of the turbidity caused by agglutination can be measured optically and is proportional to the amount of Kappa FLC or Lambda FLC in the sample. The instrument calculates the Kappa FLC or Lambda FLC concentration by interpolation of obtained signal of a 6-point calibration curve prepared from calibrators of known concentrations.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Optilite Freelite Kappa Free Kit using Binding Site Optilite analyzer
Optilite Freelite Lambda Free Kit using Binding Site Optilite analyzer

B Predicate 510(k) Number(s):

K150658

C Comparison with Predicate(s):

Device & Predicate Device(s):	K220001	K150658
Device Trade Name	Diazyme Human Kappa Free Light Chain Assay Diazyme Human Lambda Free Light Chain Assay	Freelite Human Kappa Free Kit Freelite Human Lambda Free Kit
General Device Characteristic Similarities		
Analyte	Kappa FLC Lambda FLC	Same
Measurement	Quantitative	Same
Detection Method	Latex particle immunoturbidimetric	Same
Sample type	Serum	Same
General Device Characteristic Differences		
Intended Use/ Indications For Use	The Diazyme Human Kappa Free Light Chain Assay is intended as a latex particle enhanced immunoturbidimetric assay for the quantitative determination of Kappa Free Light Chain (FLC) concentration in serum on validated analyzers. The measurement of Kappa FLC in conjunction with Lambda FLC aids in the diagnosis and monitoring of multiple myeloma in conjunction with other laboratory and clinical findings. For in-vitro diagnostic use only. The Diazyme Human Lambda Free Light Chain Assay is intended as a latex particle enhanced immunoturbidimetric assay for the quantitative determination of Lambda Free Light Chain (FLC) concentration in serum on validated analyzers. The measurement of Lambda FLC in conjunction with Kappa FLC aids in the diagnosis and monitoring of multiple myeloma in conjunction with other laboratory and clinical findings. For in-vitro diagnostic use only.	The Optilite Freelite Kappa Free Kit is intended for the quantitative in vitro measurement of kappa free light chains in serum using the Binding Site Optilite turbidimetric analyser. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings. The Optilite Freelite Lambda Free Kit is intended for the quantitative in vitro measurement of kappa free light chains in serum using the Binding Site Optilite turbidimetric analyser. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings.
Instrument	Roche cobas c501	Binding Site Optilite analyzer

Detection Antibody	Polyclonal anti-Human Kappa/ anti-human Lambda Free light chain Ig fraction coated on polystyrene latex microparticles.	Polyclonal monospecific antibody coated onto polystyrene latex
Analytical Measuring Range	Kappa FLC: 4.5–150 mg/L 90–3,000 mg/L (extended)	Kappa FLC: 2.9–127 mg/L 0.6–63500 mg/L (extended)
	Lambda FLC: 6.1–200 mg/L 122–4,000 mg/L (extended)	Lambda FLC: 52–1390 mg/L 1.3–139000 mg/L (extended)
Reference range	Kappa: 2.37 – 20.73 mg/L Lambda: 4.23 – 27.69 mg/L K/L Ratio: 0.22 – 1.74	Kappa: 3.30 – 19.40 mg/L Lambda: 5.71 – 26.30 mg/L K/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:

   Refer to K153394 and K181438

2. Linearity:

   Refer to K153394 and K181438

3. Analytical Specificity/Interference:

   Refer to K153394 and K181438

4. Assay Reportable Range:

   Refer to K153394 and K181438

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

   Refer to K153394 and K181438

6. Detection Limit:

   Refer to K153394 and K181438

7. Assay Cut-Off:

   See expected values/reference range

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Refer to K153394 and K181438

2. Matrix Comparison:

   Not applicable

C Clinical Studies:

1. Clinical Sensitivity and Specificity:

   The clinical performance of the Diazyme Kappa FLC and Lambda FLC Assays as aid in monitoring of disease status in subjects diagnosed with multiple myeloma (MM) and light chain multiple myeloma (LCMM) was investigated in a clinical study using archived serial serum samples tested by the candidate devices in multicenter sites. A total of 169 MM subjects including 22 LCMM subjects from three sites were enrolled in the 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) guideline as determined by the clinicians.

   The patient inclusion and exclusion criteria were as follows:

   Inclusion criteria:
   - Confirmed diagnosis of MM or LCMM
   - At least three blood collections per patient
   - Clinical information of response level available

   Exclusion criteria:
   - Less than three blood collections
   - MGUS patients

   Of the 169 MM subjects, 94 subjects were diagnosed with IgG Kappa (IgGK), 32 IgG Lambda (IgGL), 20 IgA Kappa (IgAK), 11 IgA Lambda (IgAL), 1 IgM Kappa (IgMK), 1 IgM Lambda (IgML), and 22 Light Chain Multiple Myeloma (13 LCMM-Kappa and 9 LCMM-Lambda). Twelve of 169 subjects had two subtypes (clones) as follows: six LCMM Kappa/IgGK; one LCMM Lambda/IgGL; one IgGK/LCMM Kappa; one IgGL/LCMM Lambda; one IgAK/LCMM Kappa; one IgAK/IgGK; and one IgML/LCMM Lambda.

   Ninety (90) subjects (53%) were male and 79 (47%) were female. The median age was 66 years old with the age ranging from 43 to 93 years old. The majority of the subjects were

African American (n=77; 45.6%). The remaining subjects were: Caucasian (n=42; 24.9%,), Asian (n=20; 11.8%); Caucasian/Hispanic (n=4; 2.4%); African/Asian (n=1; 0.6%); South Asian Indian (n=1; 0.6%); Other (n=9; 5.3%) and unknown (n=15; 8.9%). A total of 541 blood draws including 169 baselines and a total of 372 monitoring observations were tested by the Diazyme Human Kappa FLC and Lambda FLC Assays. The number of draws per subject ranged from three to nine draws. The duration of the monitoring days ranged from 10 days to 1002 days (with a median of 203 days).

The information collected for each sample included the following: (a) general information including patient's demographic information and date blood sample was drawn; (b) clinical information including patient's diagnosis and treatment initiated, and diagnostic response criteria; c) bone imaging when available and laboratory data including hypercalcemia, renal failure, anemia, and bone disease (CRAB), bone marrow plasma cell count greater than 10 percent, serum electrophoresis results (M-protein), serum immunofixation electrophoresis.

The clinical assessment for each monitoring observation as determined by the clinicians according to International Myeloma Working Group (IMWG) Version 1.2020/National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Multiple Myeloma and categorized into one of seven response categories: Stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minimal Response (MR), Stable Disease (SD), and Progressive Disease (PD).

For each of 372 monitoring observations, the percentage change of the Involved FLC Kappa (iFLC Kappa) or Involved FLC Lambda (iFLC Lambda) to not involved FLC (niFLC) was calculated by comparing the test result to the test result from the previous visit. The results of Diazyme Kappa and Lambda FLC assay in combination with other laboratory results were used to assign a response category and compared to the clinical assessment according to the following table:

	Response Criteria based on Diazyme FLC, SPE, IFE Results
Good Response	FLC ratio normal, M protein not detectable and IFE negative[#]
Moderate Response	≥ 50 to ≥ 90% reduction of rd_dFLC* and ≥ 50 to ≥ 90% reduction of M protein
Stable Disease	49% reduction to 25% increase of rd_dFLC and 49% reduction to 25% increase of M protein
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

[#] Applies only to MM population

* rd_dFLC = (dFLC t2 - dFLC t1) / dFLC t1 (while rd = relative difference; dFLC = iFLC – ni FLC; t1 = time point 1; t2 = time point 2;

^ d_dFLC = dFLC t2 - dFLC t1; dFLC = iFLC - niFLC (while iFLC = involved FLC; niFLC = not involved FLC)

Results:

The clinical performance of the Diazyme Human Kappa and Lambda FLC assays in combination with other laboratory tests as an aid in monitoring of MM 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 the Diazyme Human Kappa and Lambda FLC based on changes between the consecutive blood draws. The results are summarized in the following tables.

Response based on Diazyme FLC Assay	**Clinical Assessment**				
	Good Response**	**Moderate Response*****	**Stable Disease**	**Progressive Disease**	**Total**
Good Response	44	6	8	0	58
Moderate Response	2	27	27	6	62
Stable Disease	25	12	173	20	230
Progressive Disease	0	0	5	17	22
Total	71	45	213	43	372
Concordance (n/N) (95% CI)*	62% (44/71) (50.7%;73.2%)	60% (27/45) (46.7%; 73.3%)	81% (173/213) (76.1%; 86.4%)	40% (17/43) (25.6%; 55/8%)	70% (261/372) (65.5%; 74.5%)

* 95% CI was calcuated by bootstrap method
** Including subjects with sCR and CR
*** Including subjects with VGPR, PR and MR.

The clinical sensitivity and specificity based on "Progression" and "No-progression" are summarized in the following table. 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.

		Clinical Assessment		
		Progression	**No Progression**	**Total**
Change in Diazyme FLC	**PD***	17	5	22
	No-PD	26	324	350
	Total	43	329	372
Clinical Sensitivity: 40% (17/43) (95% CI: 25.6% to 55.8%) Clinical Specificity: 98% (324/329) (95% CI: 97.3% to 99.7%)				

* PD: ≥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

2. Other Supportive Data:

In this clinical study, all samples were also tested with the predicate device (Binding Site Optilite Freelite Kappa and Freelite Lambda Free Kit). The clinical performance of the Diazyme Human Kappa/Lambda FLC Assays as an aid in monitoring of MM patients was

compared to the predicate device based on “Progression” and “No-progression”. The results are summarized in the following table.

Diazyme Human Kappa/Lambda FLC		Optilite Freelite Kappa/Lambda FLC	
Sensitivity (n/N) (95% CI*)	**Specificity (n/N) (95% CI*)**	**Sensitivity (n/N) (95% CI*)**	**Specificity (n/N) (95% CI*)**
40% (17/43) (25.6%; 55.8%)	98% (324/329) (97.3%; 99.7%)	44% (19/43) (30.2%; 60.5%)	97% (320/329) (95.4%; 98.8%)

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

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Refer to K153394 and K181438

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.