510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k180074

B. Purpose for Submission:

New device

C. Measurand:

Lipoprotein (a) [Lp(a)]

D. Type of Test:

Quantitative immunoturbidimetric assay

E. Applicant:

Diazyme Laboratories, Inc.

F. Proprietary and Established Names:

Diazyme Lipoprotein(a) Assay

G. Regulatory Information:

Regulatory Description	Classification	Regulation	Product Code	Panel
Low Density Lipoprotein Immunological Test System	II	21 CFR 866.5600	DFC	Immunology (82)

H. Intended Use:

1. Intended use(s):

   See indication(s) for use below.

2. Indication(s) for use:

   The Diazyme Lipoprotein (a) Assay is intended as a latex particle enhanced

immunoturbidimetric assay for the in vitro quantitative determination of lipoprotein(a) [Lp(a)] concentration in human serum or plasma on Clinical Chemistry Systems. The measurement of Lipoprotein (a) is useful in evaluating lipid metabolism disorders and assessing atherosclerotic cardiovascular diseases in specific populations, when used in conjunction with clinical evaluation. For in vitro diagnostic use only

3. Special conditions for use statement(s):

For prescription use only.

Harmonization efforts for Lp(a) assay methods have suggested an impact of Apo A size heterogeneity on Lp(a) measurement methods. The effects of the impact of Apo A size have not been assessed for this assay.

Clinical assessment should be based on patient history, clinical findings and other laboratory tests.

4. Special instrument requirements:

The assay performance was established on the Beckman Coulter AU400 chemistry analyzer.

I. Device Description:

Lipoprotein(a) Reagent Composition:
    Reagent 1 - Tris Buffer Solution
    Reagent 2 - Latex particles coated with anti-Lp(a) antibodies

Reagent Preparation:
    The Lp(a) assay reagent provided is ready to use.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Diazyme Lipoprotein(a) Assay

2. Predicate 510(k) number(s):

k082488

3. Comparison with predicate:

Similarities		
Item	Candidate Device k180074	Predicate Device k082488
Intended Use	For the in vitro quantitative determination of lipoprotein(a) [Lp(a)] concentration in human serum or plasma.	Same
Test Principle	The Diazyme Lipoprotein (a) Assay is based on a latex enhanced immunoturbidimetric assay. Lp(a) in the sample binds to specific anti-Lp(a) 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 Lp(a) in the sample.	Same
Measuring Range	5.4 – 100 mg/dL	Same

Differences		
Item	Candidate Device k180074	Predicate Device k082488
Specimen Type	Human serum, EDTA plasma and lithium heparin plasma	Human serum and EDTA plasma

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; Approved Guideline.

CLSI EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition.

CLSI EP9-A3: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition.

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition.

L. Test Principle:

The Diazyme Lipoprotein (a) Assay is a latex enhanced immunoturbidimetric assay. Lp(a) in the sample binds to specific anti-Lp(a) 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 Lp(a) in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*
   The precision of the Diazyme Lipoprotein(a) Assay was evaluated following the recommendations in CLSI EP05-A2. In the study, five levels of serum specimens containing 8, 16, 21, 58, and 96 mg/dL Lp(a) respectively were tested with 2 runs per day in duplicate over 20 working days on one Beckman Coulter AU400 using three lots of the reagents. The results of the within-run, between-run, between-day, and total precision for one representative lot are shown below:

Sample	Mean mg/dL (N=80)	Within-Run		Between-Run		Between-Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum 1	8.6	0.21	2.4	0.15	1.7	0.72	8.4	0.76	8.9
Serum 2	15.3	0.43	2.8	0.00	0.0	0.66	4.3	0.78	5.1
Serum 3	21.02	0.59	2.8	0.11	0.5	1.12	5.3	1.27	6.0
Serum 4	57.9	0.91	1.6	0.00	0.0	1.23	2.1	1.53	2.6
Serum 5	96.4	0.68	0.7	0.60	0.6	1.03	1.1	1.37	1.4

The lot to lot imprecision was calculated and is shown below:

Sample	Mean mg/dL (N=240)	Between Lot	
		SD	%CV
Serum 1	7.9	0.79	10.1
Serum 2	14.6	0.91	6.2
Serum 3	20.1	1.18	5.8
Serum 4	57.6	1.64	2.8
Serum 5	95.9	1.43	1.5

   b. *Linearity/assay reportable range:*

   A linearity study was conducted following the recommendations in the CLSI guideline EP6-A. A dilution series was prepared by diluting a serum control containing approximately 100 mg/dL Lp(a) with saline to test 11 samples with concentrations ranging from 0.2 to 102.6 mg/dL. Samples were measured in triplicate on a Beckman Coulter AU400 analyzer using 3

reagent lots. The following regression equation was obtained.

$$y = 1.0314x - 0.2189 \qquad r^2 = 0.9975$$

The maximum deviation from linearity observed in the study was 7%. The studies support the sponsor's claimed measuring range of 5.4 to 100 mg/dL.

The sponsor provided data to support the claim that no high dose hook effect is observed with this assay for Lp(a) concentrations up to 500 mg/dL.

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

The Diazyme Lipoprotein(a) calibrators are traceable to the predicate device.

d. *Detection limit:*

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) of the Diazyme Lipoprotein(a) Assay were determined following the recommendations in the CLSI EP17-A2 guideline on a Beckman Coulter AU400 analyzer. To determine the LoB of the assay, a blank sample (7.5% BSA) was tested with 20 replicates for each day for three days on 1 instrument and 3 reagent lots. The LoB was calculated as the mean of the 57th and 58th highest values for the blanks. To determine the LoD of the assay, five low samples were tested with 4 replicates each for each day for three days on 1 instrument and 3 reagent lots. The following equation was used to calculate the LoD: LoD = LoB + (1.645* SD of low samples). The LoQ was determined using 6 samples ranging from 0.34 to 18.89 mg/dL tested with 8 replicates for each day for 5 days on 1 instrument and 3 reagent lots and using a fitted curve to determine the value where the upper 95% confidence interval for the curve has a CV of 20%. The results obtained are as follows are are based on the lot with the highest estimate:

- The LoB is 0.40 mg/dL
- The LoD is 1.3 mg/dL
- The LoQ is 3.2 mg/dL

e. *Analytical specificity:*

To determine potential interference from endogenous substances, two levels of Lp(a), 17 mg/dL and 43 mg/dL, were spiked with varied concentrations of potential interferents following the recommendations in the CLSI EP07-A2 guideline. No interference was defined by the sponsor as less than ± 10% deviation from the expected result.

The following substances produced less than 10% deviation from the expected results when tested at levels equal to the concentrations listed below:

Interferent	Concentration
Triglycerides	1000 mg/dL
Ascorbic Acid	176 mg/dL
Bilirubin	40 mg/dL
Bilirubin Conjugated	40 mg/dL
Hemoglobin	1000 mg/dL

 f. *Assay cut-off:*

 Not applicable.

2. Comparison studies:

 a. *Method comparison with predicate device:*

 Correlation studies were performed using 99 unaltered human serum samples ranging from 6.1 to 93.2 mg/dL tested in singlicate using both the candidate assay on a Beckman Coulter AU400 and an existing commercial Lp(a) method. One lot of reagent was used. The results were compared using linear regression analysis. The correlation coefficient (r^2) between the two methods was 0.9868, slope was 0.9828, and y intercept was 1.0033.

 b. *Matrix comparison:*

 To evaluate the anticoagulant effects, both K_2EDTA plasma and lithium heparin plasma samples were evaluated. The Lp(a) levels of 37 paired serum/K_2EDTA plasma samples (with concentrations ranging from 8.9 to 83.5 mg/dL) and 33 paired serum/lithium heparin plasma samples (with concentrations ranging from 7.2 to 88.5 mg/dL) were tested on a Beckman Coulter AU400 using 1 reagent lot. The test matrix and the comparator matrix (serum) were both tested in singlicate. The results were analyzed using linear regression and are summarized below:

 EDTA plasma/serum   *y*=0.9802*x* – 0.8104 r^2 =0.9962

 Lithium heparin plasma/serum   *y*=0.9434*x* – 0.9932 r^2 =0.9876

3. Clinical studies:

 a. *Clinical Sensitivity:*

 Not applicable.

b. *Clinical specificity:*

   Not applicable.

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

   Not applicable.

4. Clinical cut-off:

   Not applicable.

5. Expected values/Reference range:

   The following information is provided in the labeling:

   The expected range for Lp(a) has been reported to be between 10 and 30 mg/dL[1,2]. Some studies have indicated that Lp(a) concentrations in African Americans may differ from Caucasians with higher ranges observed in African Americans[3,4]. Increased serum Lp(a) concentrations are associated with an increased risk of premature coronary artery disease and stroke. Because Lp(a) levels are highly heritable, Lp(a) may be an important marker for premature CHD, especially among Caucasians. Although Lp(a) levels are higher in African Americans than in Caucasians, associated CHD risk appears to be less[5]. Each laboratory, however, is recommended to establish a range of normal values for the population in their region. Lp(a) values should be interpreted in conjunction with clinical evaluation and other lipoprotein tests when assessing atherosclerotic cardiovascular disease in specific populations.

   [1] Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. Atherosclerosis 1981; 38: 51-61.
   [2] Armstrong VW, Cremer P, Eberle E, Manke A, Schulze F, Wieland H, Kreuzer H, Seidel D. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis. Atherosclerosis 1986; 62: 249-257.
   [3] Dati F, Tate JR, Marcovina SM and the IFCC Working Group for Lp(a) Assay Standardization. First WHO/IFCC International Reference Reagent Lp(a) for Immunoassay-Lp(a) SRM 2B. Clin Chem Lab 2004; 42(6): 670-676.
   [4] Marcovina SM, Albers JJ, Jacobs DR, Perkins LL, Lewis CE, Howard, BV and Savage P. Lp(a) and Apo (a0 Phenotypes in Caucasians and African Americans. The Cardia Study. Arteriosclerosis and Thrombosis. 1993; 13(7): 1037-1045.
   [5] Wu, Alan HB. Tietz Clinical Guide to Laboratory Tests. 4th edition. 2006; 678-9.

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.