

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

A. 510(k) Number:

k123046

B. Purpose for Submission:

New device

C. Measurand:

Lipoprotein (a) [Lp(a)]

D. Type of Test:

Quantitative immunoturbidimetric assay

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

ADVIA® Chemistry Lipoprotein(a) Assay
ADVIA® Chemistry Lipoprotein(a) Calibrator

G. Regulatory Information:

<u>Product</u>	<u>Classification</u>	<u>Regulation</u>	<u>Panel</u>
<u>DFC</u>	<u>Class II</u>	<u>21 CFR 866.5600</u> <u>Low Density Lipoprotein</u> <u>Immunological Test System</u>	<u>Clinical Chemistry(75)</u>
<u>JIT</u>	<u>Class II</u>	<u>21 CFR 862.1150</u> <u>Calibrator, Secondary</u>	<u>Clinical Chemistry (75)</u>

H. Intended Use:

1. Intended use(s):

For *in vitro* diagnostic use in the quantitative measurement of lipoprotein (a) (Lp(a)) in human serum or plasma on the ADVIA Chemistry systems. Measurement of Lp(a) may aid in the diagnosis of disorders of lipid (fat) metabolism and assessing persons at risk for cardiovascular diseases when used in conjunction with clinical evaluation and other lipoprotein tests.

The ADVIA® Chemistry Lipoprotein (a) calibrator is intended for use in the calibration of ADVIA® Chemistry systems for the ADVIA Chemistry Lipoprotein(a) (LPA) assay.

2. Indication(s) for use:

See intended use.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

For use on the ADVIA 1650 Analyzer

I. Device Description:

The Lipoprotein(a) reagents are ready-to-use liquid reagents packaged for use on the automated ADVIA 1650 Chemistry system. They are supplied as a 100 tests/wedge, 2 wedges/kit. The kit includes two reagents, R1 and R2. R1 is glycine-EDTA buffer. R2 is a suspension of latex particles coated with anti-human Lp(a) antibodies (rabbit) in glycine buffer.

ADVIA Chemistry Lipoprotein(a) calibrator is a single analyte, human serum based product containing human lipoprotein (a). The kit consists of 1 vial each of 5 calibrator levels which are lyophilized. The volume per vial (after reconstitution with deionized water) is 1.0 mL. Deionized water is recommended to be used as a zero calibrator.

Contains human source material. While each human serum or plasma donor unit used in the manufacture of this product was tested by FDA-approved methods and found nonreactive for hepatitis B surface antigen, hepatitis C antigen, and antibody to HIV-1/2, all products manufactured using human source material should be handled as potentially infectious.

J. Substantial Equivalence Information:

1. Predicate device name(s) and number(s):

Randox Lipoprotein(a) assay
k011568

Radox Lipoprotein(a) Calibrator Series
k011568

2. Comparison with predicate:

Similarities		
Characteristic	New Device ADVIA Chemistry Lipoprotein(a)	Predicate Device Radox Lipoprotein(a) assay (k011568)
Intended Use	Same	Immunoturbidimetric assay for the quantitative <i>in vitro</i> determination of Lipoprotein(a) in human serum or plasma.
Principle	Same	Lp(a) in sample binds to specific anti-Lp(a) antibodies that are coated on latex particles. Lp(a) binding causes agglutination of the latex particles. The amount of agglutination is readout optically via sample turbidity and is directly proportional to the amount of Lp(a) in the sample.

Differences		
Characteristic	New Device ADVIA Chemistry Lipoprotein(a)	Predicate Device Radox Lipoprotein(a) assay (k011568)
Instrument	ADVIA 1650 Chemistry	Hitachi 717 Analyzer
Measuring Range	10-85 mg/dL	2-90 mg/dL

Similarities		
Characteristic	New Device ADVIA Chemistry Lipoprotein(a) Calibrator	Predicate Device Randox Lipoprotein(a) Calibrator Series (k011568)
Intended Use	Same	Used for calibration of Lp(a) assay
Form	Same	Lyophilized

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

Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition (CLSI EP07-A2)

Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (CLSI EP17-A)

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

L. Test Principle:

In the ADVIA Chemistry Lipoprotein(a) assay, sample is diluted and then mixed with the R1 reagent (a buffer), followed by an addition of the R2 reagent (which contains latex particles coated with antibodies specific for Lipoprotein (a). The formation of the antibody-antigen complex during the reaction results in an increase in turbidity. This turbidity is measured at 694 nm.

M. Performance Characteristics (if/when applicable):

All studies were performed on the ADVIA 1650 Analyzer

1. Analytical performance:
 - a. *Precision/Reproducibility:*

The precision of the Siemens Lp(a) assay was evaluated according to CLSI document EP05-A2. In this study, 2 human serum pools spiked with Lp(a) to final concentrations 50 and 80 mg/dL and 3 samples of a serum-based control material with approximate Lp(a) concentrations 7, 13 and 18 mg/dL were assayed 2 times per run at 2 runs a day for 20 days. Experiments were performed using two reagent lots on two ADVIA 1650 Analyzers . The sponsor provided representative results from a single lot that are included in the table below.

Sample	MEAN (mg/dL)	Within Run		Between Run		Between Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 2	14.17	0.12	0.9	0.12	0.8	0.08	0.5	0.19	1.3
Control 3	18.44	0.14	0.7	0.12	0.6	0.07	0.4	0.20	1.1
Serum Pool 1	49.75	0.40	0.8	0.43	0.9	0.30	0.6	0.66	1.3
Serum Pool 2	83.67	1.03	1.2	0.85	1.0	0.00	0.0	1.34	1.6

b. *Linearity/assay reportable range:*

The sponsor assessed linearity with one run using one lot of reagents with each sample tested in triplicate. Nine diluted samples with Lp(a) concentrations evenly distributed were prepared by mixing a high Lp(a) concentration serum pool and a low Lp(a) concentration serum pool in varying amounts. This yielded linearity samples with Lp(a) levels that spanned a range from 7.75 to 102.30 mg/dL.

The sponsor calculated linear regressions from mean observed versus expected value using an unweighted regression model and observed maximum % difference from observed values versus linear fit of 4%.

The fitted linear model is:

$$\text{Serum: } y = -0.18 + 0.99x$$

where $y = \text{Lp(a) (mg/dL)}$ and $x = \text{expected concentration}$.

The studies supported the sponsor's claimed measuring range of 10 – 85 mg/dL.

High Dose Hook Effect

Sponsor performed additional hook effect studies and demonstrated no hook effect up to Lp(a) concentrations of 493 mg/dL.

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

Calibrators are traceable to in-house Master Lot calibrators of human Lp(a) prepared volumetrically in human serum and value assigned via method comparison to a commercially available device.

Each lot of calibrators is then traceable to the Master Lot via the ADVIA

Lp(a) assay tested in multiple replicates. Newly value assigned lot calibrators are then confirmed through use in the Lp(a) assay by creating a calibration curve and then testing Master Lot, calibrators and controls against this calibration curve.

Reagent shelf life and on board stability protocols and acceptance criteria were provided and found acceptable.

Calibrators are the same material as cleared in k011568. The claimed shelf life (closed) is 36 months. The sponsor demonstrated open vial stability of 14 days at 2-8°C.

d. Detection limit:

LoB, LoD and LoQ studies were performed based upon CLSI EP-17A.

LoB Test Protocol

One blank sample was tested on two analyzers with 2 reagent lots for 4 replicates per run at 2 runs per day for 5 days yielding a total of 40 measurements per lot/analyzer.

LoB was defined as the concentration at which there is a 95% probability that the sample is analyte-free and was calculated as the 95th percentile of 40 runs.

LoD Test Protocol

Five samples of the LoB pool were spiked with Lp(a) to yield samples with low analyte concentrations of 3.6, 4.8, 7.2 and 9.6 mg/dL were measured on 2 analyzers using 2 reagent lots for 4 replicates per run at 2 runs per day for 5 days yielding a total of 40 measurements per lot/analyzer.

LoD was then calculated nonparametrically as the lowest level material in which the 5th percentile equals or exceeds the LoB.

LoQ Test Protocol

LoQ was determined from the same 40 point data set used to generate LoD with an observed bias of 12.4%. Sponsor provided data to support LoQ = LoD.

Based on linearity studies and detection limit studies the sponsor provided data to support the following claims:

LoB = 6.0 mg/dL

LoD = 9.0 mg/dL

LOQ = 10.0 mg/dL

e. Analytical specificity:

Testing was performed according to CLSI EP07- to determine whether the presence of hemoglobin, triglycerides (using Intralipid as a mimic), conjugated and unconjugated Bilirubin may interfere with assay results.

Three human sera samples were used with Lp(a) concentrations of 15, 30 and 50 mg/dL. Each sample level was spiked with increasing amounts of interferents for a total of 5 samples with interferent with controls samples at each level that were not spiked. Then the spiked and unspiked samples were tested in duplicate and used to calculate % recovery (measured concentration compared to Lp(a) concentration with zero interferent). Lp(a) recovery of $\pm 10\%$ of reference value was defined as acceptable by the sponsor.

Substance	Tested Concentration
Hemoglobin	Up to 1000 mg/dL
Intralipid	Up to 1000 mg/dL
Bilirubin (conj)	Up to 60 mg/dL
Bilirubin (unconj)	Up to 60 mg/dL

The sponsor provided information that the apo(a) isoforms that are heterogenous with respect to size do not interfere with the assay. The assay gives an accurate test result for Lp(a) across apo(a) isoforms. The sponsor also provided information that plasminogen and apolipoprotein B do not interfere with the assay up to concentrations of 150 mg/dL and 225 mg/dL respectively.

f. *Assay cut-off:*
Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

To characterize correlation to the predicate, a method comparison study was performed with 68 human sera samples with concentrations ranging from 11 – 81.6 mg/dL tested by the Siemens ADVIA Lp(a) Assay (expressed as mg/dL) and predicate on the Hitachi 717 (expressed as mg/dL). Samples were tested in duplicate and the first replicate analyzed by linear regression.

Data were analyzed by least squares linear regression with 95% CI indicated in parentheses:

slope = 1.01 (1.00 – 1.02)
intercept = - 1.02 (-1.47 – 0.57)
r = 0.99

b. Matrix comparison

To characterize correlation to the predicate for lithium heparin plasma, a method comparison study was performed with 44 human plasma samples with Lp(a) concentrations ranging from 12 – 80.1 mg/dL tested by the Siemens ADVIA Lp(a) Assay (expressed as mg/dL) and the predicate device on the Hitachi 717 (expressed as mg/dL). Samples were tested in duplicate and the first replicate analyzed by linear regression.

Data were analyzed by least squares linear regression with 95% CI indicated in parentheses:

slope = 1.01 (0.99 – 1.02)
intercept = -0.98 (-1.49 – -0.47),
r = 0.99.

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 sponsor states the individual concentration of Lp(a) in the serum depends on genetic factors. The range of variation in a population is relatively large.¹ Lp(a) values are known to vary with ethnicity. The sponsor recommends a cutoff for this assay of < 30 mg/dL, however this is to be considered as a guideline. It is also recommended that each laboratory should determine its own reference ranges for the diagnostic evaluation of patient results.

N. Proposed Labeling:

¹ Koschinsky ML, Marcovina SM. Lipoprotein(a): structural implications for pathophysiology. *Int J Clin Lab Res.* 1997; 27:14-23.

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.