DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

September 7, 2016

SIEMENS HEALTHCARE DIAGNOSTICS, INC.
KATHLEEN DRAY-LYONS
REGULATORY AND CLINICAL AFFAIRS SPECIALIST
500 GBC DRIVE
NEWARK DE 19714

Re: K160724
Trade/Device Name: ADVIA Chemistry® Creatine Kinase (CK_L) Assay,
ADVIA Chemistry® Enzyme 3 Calibrator
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: II
Product Code: CGS, JIT
Dated: August 2, 2016
Received: August 3, 2016

Dear Kathleen Dray-Lyons:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K160724

Device Name
ADVIA Chemistry® Creatine Kinase (CK_L) Assay
ADVIA Chemistry® Enzyme 3 Calibrator

Indications for Use *(Describe)*

ADVIA Chemistry® Creatine Kinase (CK_L) Assay:
The ADVIA Chemistry® Creatine Kinase (CK_L) assay is for in vitro diagnostic use in the quantitative determination of creatine kinase activity in human plasma (lithium heparin) or serum on ADVIA Chemistry systems. The assay can be used to aid in the diagnosis and treatment of myocardial infarction and muscle diseases, such as Duchenne progressive muscular dystrophy.

ADVIA Chemistry® Enzyme 3 Calibrator:
ADVIA Chemistry® Enzyme 3 Calibrator is intended for in vitro diagnostic use in the calibration of the ADVIA Chemistry Creatine Kinase (CK_L) assay on the ADVIA Chemistry systems.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of SMDA 1990 and 21 CFR §807.92.

The assigned 510(k) number is: K160724

1. Manufacturer's Name, Address, Telephone, and Contact Person, Date of Preparation

Applicant: Siemens Healthcare Diagnostics Inc.
500 GBC Drive
Newark, DE 19714

Contact Information: Siemens Healthcare Diagnostics Inc.
P.O. Box 6101
Newark, DE 19714
Attn: Kathleen Dray-Lyons
Tel: 781-826-4551
Email: kathleen.a.dray-lyons@siemens.com

Date of Preparation: September 6, 2016

2. Device Names:

- ADVIA Chemistry® Creatine Kinase (CK_L) Assay
- ADVIA Chemistry® Enzyme 3 Calibrator

Classification:

- 21 CFR §862.1215; Creatine phosphokinase/creatine kinase or isoenzymes test system, Class II
- 21 CFR §862.1150; Calibrator Secondary, Class II

Product Code:

- CGS
- JIT

Panel:

- Clinical Chemistry
- Clinical Chemistry

3. Identification of the Predicate Devices:

ADVIA Chemistry Creatine Kinase (CKNAC) Assay - K991576
Dimension Vista ENZ 6 CAL - K083579

4. Device Description:

ADVIA Chemistry Creatine Kinase Assay:
ADVIA Chemistry Creatine Kinase (CK_L) assay is a ready-to-use liquid reagent packaged for use on the automated ADVIA Chemistry systems. Creatine Kinase reacts with creatine phosphate and ADP to form adenosine triphosphate (ATP), which is coupled to the hexokinase-G6PD reaction, generating NADPH. The concentration of NADPH is measured by the increase in absorbance at 340/596 nm.

ADVIA Chemistry ENZ 3 CAL:
ENZ 3 CAL is a liquid frozen human serum albumin based product containing creatine kinase MM from human heart. Enzyme 3 Calibrator kit consists of six vials of the same calibrator which is ready for use (no preparation is required).

5. Device Intended Use:

ADVIA Chemistry Creatine® Kinase (CK_L) Assay:
The ADVIA Chemistry® Creatine Kinase (CK_L) assay is for *in vitro* diagnostic use in the quantitative determination of creatine kinase activity in human plasma (lithium heparin) or serum on ADVIA Chemistry systems. The assay can be used to aid in the diagnosis and treatment of myocardial infarction and muscle diseases, such as Duchenne progressive muscular dystrophy.

ADVIA Chemistry ENZ 3 CAL:
ADVIA Chemistry® Enzyme 3 Calibrator is intended for *in vitro* diagnostic use in the calibration of the ADVIA Chemistry Creatine Kinase (CK_L) assay on the ADVIA Chemistry systems.

6. Medical device to which equivalence is claimed:

ADVIA Chemistry Creatine® Kinase (CK_L) Assay:
The modified ADVIA Chemistry CK_L assay is substantially equivalent in intended use and technology to the predicate ADVIA Chemistry Creatine Kinase (CKNAC**)** assay cleared under K991576. Both assays utilize creatine kinase, which reacts with creatine phosphate and ADP to form ATP that is coupled to the hexokinase-G6PD reaction, generating NADPH. The concentration of NADPH is measured by the increase in absorbance. A comparison of the similarities and differences between the currently marketed ADVIA Chemistry CKNAC (predicate) versus the proposed modified ADVIA Chemistry CK_L assay is provided in the table below.

Similarities and Differences
ADVIA Chemistry CK Assay (K991576) versus
Modified ADVIA Chemistry CK_L Assay

Feature	Predicate ADVIA Chemistry CKNAC K991576	Proposed ADVIA Chemistry CK_L Modified Device
Intended Use Statement	For *in vitro* diagnostic use in the quantitative determination of creatine kinase activity in human serum and plasma on the ADVIA Chemistry systems. Such measurements are used mainly in the diagnosis and treatment of myocardial infarction and muscle diseases such as Duchenne progressive muscular dystrophy.	The ADVIA Chemistry® Creatine Kinase (CK_L) assay is for in vitro diagnostic use in the quantitative determination of creatine kinase activity in human plasma (lithium heparin) or serum on ADVIA Chemistry systems. The assay can be used to aid in the diagnosis and treatment of myocardial infarction and muscle diseases, such as Duchenne progressive muscular dystrophy.
Principle	Creatine Kinase reacts with creatine phosphate and ADP to form ATP which is coupled to the hexokinase-G6PD reaction, generating NADPH. The concentration of NADPH is measured by the increase in absorbance at 340/410 nm.	Creatine Kinase reacts with creatine phosphate and ADP to form ATP which is coupled to the hexokinase-G6PD reaction, generating NADPH. The concentration of NADPH is measured by the increase in absorbance at 340/596 nm.
Kit Components	Reagent 1 - lyophilized Reagent 1 mix – lyophilized	Reagent 1 - liquid Reagent 2 - liquid
Calibrator	None – fixed calibrator value	ADVIA Enzyme 3 Calibrator
Sample Type	Serum and lithium heparin plasma	Same
Analytical Range	0 to 1300 U/L	15 to 1300 U/L
Extended Range	1300 to 7800 U/L	Same
Analyzers	ADVIA Chemistry 1650, 1200, 1800, 2400 and XPT Systems	ADVIA Chemistry 1800 System

ADVIA Chemistry ENZ 3 CAL:
The ENZ 3 CAL is substantially equivalent in intended use to the predicate Dimension Vista ENZ 6 CAL (K083579). A comparison of the similarities and differences between the currently Dimension Vista ENZ 6 CAL versus the proposed ADVIA Chemistry ENZ 3 CAL is provided in the table below.

Similarities and Differences
Dimension Vista ENZ 6 CAL (K083579) versus
ADVIA Chemistry ENZ 3 CAL

Feature	Predicate Dimension Vista® ENZ 6 CAL	Proposed ADVIA Chemistry® ENZ 3 CAL
Intended Use	The ENZ 6 CAL is an in vitro diagnostic product for the calibration of Creatine Kinase (CKI) and Creatine Kinase MB (MBI) methods on the Dimension Vista® System	ADVIA Chemistry® Enzyme 3 Calibrator is intended for *in vitro* diagnostic use in the calibration of ADVIA Chemistry Creatine Kinase (CK_L) assay on the ADVIA Chemistry® systems.
Traceable to:	IFCC Reference Method	Same
Composition	ENZ 6 CAL is a liquid frozen human serum albumin based product containing creatinine kinase BB from porcine brain and creatine kinase MM from human heart.	ADVIA Chemistry ENZ 3 CAL is a liquid frozen human serum albumin (5%) and preservatives with lot-specific concentrations of creatine kinase MM from human heart.
Packaging Content	3 vials: Calibrator A, 2mL per vial	6 vials of calibrator, 2mL per vial
Storage	-20 °C or below	-25 to -15°C

7. Performance Characteristics

Method Comparison:

A split sample method comparison between the ADVIA Chemistry CK_L assay versus the predicate ADVIA Chemistry CKNAC (K991576) assay was performed with 116 native de-identified human serum samples across the assay range (15 to 1300 U/L) on the ADVIA Chemistry 1800 system. Analysis of the results using Deming (Orthogonal) regression yielded the following:

Method	n	Predicate Method Sample Range U/L	Proposed Method Sample Range U/L	Slope (95% CI)	Intercept U/L (95% CI)	Correlation Coefficient (R)
ADVIA CKNAC versus ADVIA CK_L	116	23 to 1253	22 to 1280	1.01 (1.00 to 1.02)	-1.8 (-3.3 to -0.3)	1.00

Precision:

Testing was performed over twenty (20) days, two (2) runs per day, a single test from two (2) independent cups were analyzed for each test material using the ADVIA

Chemistry CK_L assay on the ADVIA Chemistry 1800 System. Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of CLSI EP05-A2. Typical precision is summarized below.

Repeatability and Within-Lab Results
ADVIA CK_L on the ADVIA 1800

Product	Mean U/L	Repeatability SD	Repeatability %CV	Within-Lab SD	Within-Lab %CV
BIORAD QC 1	75	1.3	1.7	1.9	2.6
BIORAD QC 2	232	1.5	0.6	3.1	1.4
BIORAD QC 3	639	2.6	0.4	8.1	1.3
PLASMA POOL 1	1202	4.7	0.4	6.3	0.5
SERUM POOL 1	85	1.7	2.0	2.9	3.4
SERUM POOL 2	194	3.0	1.5	3.2	1.7
SERUM POOL 3	938	5.2	0.6	5.6	0.6

Linearity

Linearity across the assay range was confirmed according to CLSI EP06-A, Evaluation of the Linearity of Quantitative Measurement, by testing a sample with a high concentration of creatine kinase on the ADVIA Chemistry CK_L assay and diluting it with low serum sample. Data were analyzed using weighted linear regression analysis [x-axis: theoretical concentration versus y-axis: measured concentration]. A 2nd - and 3rd -order polynomial regressions of the mean observed analyte values vs. expected concentrations were generated. These data support the measuring range of 15 to 1300 U/L. A summary of the linearity data is presented below.

Range of Samples		Linear Regression Equation	Regression Constant	R	P-Value		
Low	High				Quadratic X^2	Cubic X^2	Cubic X^3
1	1372	Y=1.00X+0.5	0.5	1.00	0.2346	0.1962	0.2610

Sample Number	Expected Results (U/L)	Observed Results (U/L)						Linear Predicted (U/L)	% Bias from the Predicted	
		Result 1	Result 2	Result 3	Mean Values	SD	CV		% Bias	Bias (U/L)
1	1	0	1	1	1	0.6	86.6	1	N/A	0
2	172	177	175	180	177	2.5	1.4	172	3	6
3	344	346	347	343	345	2.1	0.6	343	1	2
4	516	513	516	518	516	2.5	0.5	514	0	1
5	687	686	689	682	686	3.5	0.5	685	0	1
6	859	861	865	867	864	3.1	0.4	856	1	8
7	1031	1025	1023	1014	1021	5.9	0.6	1027	-1	-6

Sample Number	Expected Results (U/L)	Observed Results (U/L)						Linear Predicted (U/L)	% Bias from the Predicted	
		Result 1	Result 2	Result 3	Mean Values	SD	CV		% Bias	Bias (U/L)
8	1202	1195	1196	1197	1196	1.0	0.1	1197	0	-1
9	1374	1371	1370	1375	1372	2.6	0.2	1369	0	3

Detection Capability

The LoB and LoD values are determined with proportions of false positives (α) less than 5% and false negatives (β) less than 5%, based on 450 determinations with 225 blank and 225 low-level sample replicates.

The LoB is the highest measurement result that is likely to be observed on a blank sample. The LoB for the ADVIA Chemistry CK_L assay is 3 U/L.

The LoD is the smallest amount that this assay can reliably detect to determine presence or absence of an analyte. The LoD for the ADVIA Chemistry CK_L assay is 6 U/L.

The LoQ is the lowest amount of creatine kinase that can be determined quantitatively within a defined total error. The LoQ for the ADVIA Chemistry CK_L assay is 15 U/L.

Interference Testing

Interference testing was performed according to CLSI/NCCLS EP07-A2: Approved Guideline Interference Testing in Clinical Chemistry to determine the effect of various endogenous and exogenous substances on the ADVIA Chemistry CK_L assay. For all interferents, the percent bias was determined by testing a control sample without the interferent and comparing it to the value obtained from a test sample to which the potential interferent had been added. Interferents were tested at two levels of creatine kinase, 95 ± 14 U/L and 265 ± 40 U/L. For each spiked sample, the % recovery was determined. A summary of the non-interfering substance data is presented below.

Interference Testing
CK_L on the ADVIA 1800

Interferent	Interferent Test Concentration	CK Test Level (U/L)	% Difference
Hemolysate	125 (mg/dL)	100	7%
	125 (mg/dL)	284	1%
Bilirubin Conjugated	60 (mg/dL)	93	1%
	60 (mg/dL)	256	2%
Bilirubin Unconjugated	60 (mg/dL)	94	2%
	60 (mg/dL)	264	2%
Lipemia (Intralipid)	1000 (mg/dL)	94	5%
	1000 (mg/dL)	276	0%
Ascorbid Acid	6 (mg/dL)	91	4%

Interferent	Interferent Test Concentration	CK Test Level (U/L)	% Difference
	6 (mg/dL)	271	1%
Sulfasalazine	300 (mg/L)	94	0%
	300 (mg/L)	264	2%
Sulfapyridine	300 (mg/L)	93	1%
	300 (mg/L)	263	2%

Method Comparison versus IFCC Reference Method

A split sample method comparison between the ADVIA Chemistry CK_L assay on the ADVIA Chemistry 1800 system versus the IFCC certified reference method on the Konelab 30i analyzer (Thermo Fisher Scientific) was performed with 100 native de-identified human serum samples across the assay range (15 to 1300 U/L). Analysis of the results yielded the following:

Method	n	Predicate Method Sample Range U/L	Proposed Method Sample Range U/L	Slope (95% CI)	Intercept U/L (95% CI)	Correlation Coefficient (R)
ADVIA CK_L versus IFCC Reference Method	100	21 to 1178	16 to 1245	1.05 (1.03 to 1.07)	-6.9 (-8.8 to -4.9)	1.00

Matrix Comparison

To confirm the equivalency of sample types, the performance of the ADVIA Chemistry CK_L assay was compared for serum and lithium heparin plasma samples. Testing was performed using one lot of reagents and a single replicate from a matched set of serum and plasma samples in accordance with CLSI EP09-A3.

Specimen Type	n	Serum Sample Range U/L	Plasma (Lithium heparin) Sample Range U/L	Slope	Intercept U/L	Correlation Coefficient (R)
Serum versus Plasma	55	37–1282	39 to 1284	1.01	-0.6	1.00

8. Conclusion:

The proposed modified ADVIA Chemistry CK_L assay is substantially equivalent to the current legally marketed device based on intended use, principle and the performance characteristics above.