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

May 26, 2017

ROCHE DIAGNOSTICS
NOEL MENCIAS
REGULATORY AFFAIRS CONSULTANT
9115 HAGUE ROAD
INDIANAPOLIS IN 46250

Re: K162526
Trade/Device Name: Creatine Kinase-MB
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: II
Product Code: JHW
Dated: March 3, 2017
Received: March 6, 2017

Dear Noel Mencias:

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,

Kellie B. Kelm -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)*
k162526

Device Name
Creatine Kinase-MB

Indications for Use *(Describe)*
The Creatine Kinase-MB assay is an in-vitro test for the quantitative determination of the catalytic activity of creatine kinase MB subunit (CK-MB) in human serum and plasma on Roche/Hitachi cobas c systems.

Measurements of creatine phosphokinase and its isoenzymes are used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(k) Summary
k162526

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

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Noel B. Mencias Phone: (317) 521-3172 FAX: (317) 521-2324 Email: noel.mencias@roche.com
Date Prepared	May 23, 2017
Proprietary Name	Creatine Kinase-MB
Common Name	Creatine Kinase-MB
Classification Name	Creatine phosphokinase/creatine kinase or isoenzymes test system.
Product Codes, Regulation Numbers	JHW, 21 CFR § 862.1215
Predicate Devices	Roche CK-MB, k003158
Establishment Registration	For the Creatine Kinase-MB assay, the establishment registration number for Roche Diagnostics GmbH in Mannheim, Germany is 9610126. The establishment registration number for Roche Diagnostics in the United States is 1823260.

1. DEVICE DESCRIPTION

The Creatine Kinase-MB assay is a two reagent assay for the quantitative determination of creatine kinase-MB (CK-MB) in human serum and plasma on automated clinical chemistry analyzers. The rate of the NADPH formation is directly proportional to the catalytic CK-MB activity. It is determined by measuring the increase in absorbance photometrically.

2. INDICATIONS FOR USE

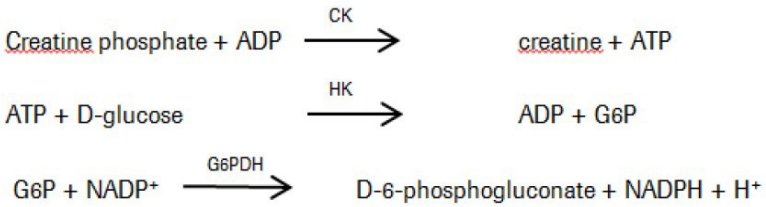
The Creatine Kinase-MB assay is an in-vitro test for the quantitative determination of the catalytic activity of creatine kinase MB subunit (CK-MB) in human serum and plasma on Roche/Hitachi **cobas c** systems.

Measurements of creatine phosphokinase and its isoenzymes are used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy.

3. TECHNOLOGICAL CHARACTERISTICS

Human CK-MB is composed of two subunits, CK-M and CK-B which both have an active site. With the aid of specific antibodies to CK-M, the catalytic activity of CK-M subunits in the sample is inhibited to 99.6 % without affecting the CK-B subunits. The remaining CK-B activity, corresponding to half the CK-MB activity, is determined by the total CK method. As the CK-BB isoenzyme only rarely appears in serum and the catalytic activity of the CK-M and CK-B subunits hardly differ, the catalytic activity of the CK-MB isoenzyme can be calculated from the measured CK B activity by multiplying the result by 2.

Figure 1: CK MB: UV test



The rate of the NADPH formation is directly proportional to the catalytic CK-MB activity. It is determined by measuring the increase in absorbance photometrically.

The following table compares the Candidate Creatine Kinase-MB with its predicate device, Roche CK-MB (k003158).

Table 1: Assay Comparison

Feature	Predicate Device Creatine Kinase-MB (k003158)	Candidate Device Creatine Kinase-MB
Intended Use	For the quantitative in vitro determination of the MB isoenzyme of creatine kinase in human serum and plasma.	Same
Test Principle	Human CK-MB is composed of two subunits, CK-M and CK-B which both have an active site. With the aid of specific antibodies to CK-M, the catalytic activity of CK-M subunits in the sample is inhibited to 99.6 % without affecting the CK-B subunits. The remaining CK-B activity, corresponding to half the CK-MB activity, is determined by the total CK method. As the CK-BB isoenzyme only rarely appears in serum and the catalytic activity of the CK-M and CK-B subunits hardly differ, the catalytic activity of the CK-MB isoenzyme can be calculated from the measured CK B activity by multiplying the result by 2. The rate of the NADPH formation is directly proportional to the catalytic CK-MB activity. It is determined by measuring the increase in absorbance photometrically.	Same

Feature	Predicate Device Creatine Kinase-MB (k003158)	Candidate Device Creatine Kinase-MB
Sample Type/Matrix	Serum and plasma, free from hemolysis. Acceptable anticoagulants are heparin and EDTA.	Serum: Non-hemolyzed serum. Plasma: Li-Heparin, K2-, K3-EDTA. Non-hemolyzed plasma.
Calibrator	Calibrator f.a.s. CK-MB	Calibrator f.a.s. CK-MB (k101456)
Calibration Interval	After reagent lot change and as required following quality control procedures	After reagent lot change and as required following quality control procedures
Traceability/Standardization	Traceable to IFCC	This method has been standardized against the IFCC Method for Creatine Kinase with addition of antibodies.
Reagent Stability	2-8 °C until expiration date	Same
Reagent On-Board Stability	28 days opened and refrigerated on the analyzer	On-board in use and refrigerated on the analyzer: 8 weeks
Measuring Range	5 – 2300 U/L (0.08 – 38..4 µkat/L)	10 – 2000 U/L (0.17-33.4 µkat/L)
Lower Limits of Measurement	LDL = 5 U/L	Limit of Blank = 3 U/L (0.05 µkat/L) Limit of Detection = 3 U/L (0.05 µkat/L) Limit of Quantitation = 10 U/L (017 µkat/L)

4. NON-CLINICAL PERFORMANCE EVALUATION

The following performance data were provided in support of the substantial equivalence determination:

Precision according to CLSI EP5-A3

Detection Limit: LoB, LoD and LoQ according to CLSI EP17-A2

Linearity according to CLSI EP6-A

Endogenous Interferences - H, L and I Indices

Endogenous Interferences - Triglycerides

Exogenous Interferences - Drugs

Method Comparison to Predicate

Matrix Comparison - Anticoagulants

4.1. Precision

4.1.1. Repeatability and Intermediate Precision

Precision experiments are performed in Accordance with CLSI Guideline EP5-A3. Two aliquots per run, two runs per day for ≥ 21 days were performed on the same analyzer using 3 lots of reagent. Repeatability (within run precision) and intermediate precision (within lab precision) were calculated. The samples were randomized in each run separately. For each sample, the following are calculated: Mean, Repeatability and intermediate precision as CV and SD values, and the upper 95% confidence interval for SD and CV values.

4.1.2. Reproducibility

Table 2: Repeatability Summary

Specimen	Mean (U/L)	SD (U/L)	CV (%)
Human Serum 1	17.9	0.4	2.2
Human Serum 2	29.1	0.4	1.2
Human Serum 3	524	2.5	0.5
Human Serum 4	1040	4.9	0.5
Human Serum 5	1826	25	1.3
PreciControl ClinChem Multi 1	41.0	0.3	0.8
PreciControl ClinChem Multi 2	99.2	0.5	0.5

Table 3: Intermediate Precision Summary

Specimen	Mean (U/L)	SD (U/L)	CV (%)
Human Serum 1	17.8	0.5	2.8
Human Serum 2	29.0	0.6	1.9
Human Serum 3	531	4.4	0.8
Human Serum 4	1040	8.4	0.8
Human Serum 5	1851	42	2.3
PreciControl ClinChem Multi 1	40.2	0.7	1.7
PreciControl ClinChem Multi 2	98.7	1.5	1.5

4.2. Analytical Sensitivity

4.2.1. Limit of Blank (LoB)

For determination of LoB one analyte free sample was measured with three lots in 10-fold determination in 6 runs, distributed over 3 days, on one **cobas c** 501 analyzer. In total, 60 measurements were obtained per lot. Data analysis is based on determination of the 95th percentile of the 60 measured values.

4.2.2. Limit of Detection (LoD)

For determination of LoD five samples with low-analyte concentration (approximately up to 4 times the LoB) were measured with three lots in twofold determination in 6 runs, distributed over 3 days, on one **cobas c** 501 analyzer. In total 60 measurements will be obtained per lot.

4.2.3. Limit of Quantitation (LoQ)

A low Level Sample Set was prepared by diluting 5 human serum samples with an analyte free diluent (0.9% NaCl). The Low level Sample Set was tested in 5 replicates per sample on 5 days, one run per day on one **cobas c** 501 analyzer.

Table 4: LoB, LoD, and Low Results

	Result (U/L)	Claim (U/L)
Limit of Blank (LoB)	0.3	3
Limit of Detection (LoD)	1.0	3
Limit of Quantitation (LoQ)	1.9	10

4.3. Linearity/Assay Reportable Range

4.3.1. Regression Analysis

The linearity study was conducted to demonstrate that measurements across the claimed measuring range for each parameter are linear. The study was performed according to CLSI guideline EP6-A.

Dilution series were prepared using the human sample pools (one serum pool and one plasma pool) with CKMB concentrations above the upper end of the measuring range. Dilutions were made using 0.9% NaCl. The dilution series contain 16 concentrations for serum and 18 dilution steps for plasma. Samples were measured in triplicate and data analysis was done separately for each sample.

Linear regression analysis was done according to EP6-A.

In a first step, a linearity check was performed with first order (linear) regression and then with higher order models (quadratic and cubic). The linear regression was not forced through the origin. The linear regression was weighted.

Table 5: Linearity Results

Sample Type	Linear Regression
Plasma	y=0.969 + 0.210 correlation coefficient (R^2)=0.9996
Serum	y=0.992x + 0.306 correlation coefficient (R^2)=0.9999

4.4. Endogenous Interferences

4.4.1. I, H, and L Indices

The effects of interference by hemoglobin, lipemia (Intralipid), Bilirubin on the CK-MB test system is determined on the **cobas c** 501 analyzer using pooled human serum samples spiked with varying levels of interferent. The resulting sample series were tested in triplicate and the mean values used to calculate % recovery, by comparing the measured concentration to the expected concentration (which is the CK-MB concentration when no interferent was added).

Table 6: Interference – I, H, and L Indices

Interferent	No Interference up to	Claim
Conjugated Bilirubin	Level 1: 76 I Index Level 2: 76 I Index	No significant interference up to an I index of 60 for conjugated and 20 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL and approximate unconjugated bilirubin concentration: 342 µmol/L or 20 mg/dL).
Unconjugated Bilirubin	Level 1: 28 I Index Level 2: 67 I Index	
Lipemia	Level 1: 753 L Index Level 2: 632 L Index	No significant interference up to an L index of 500. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Hemolysis interferes with the assay. Hemolyzed samples should not be used.

4.5. Exogenous Interferences – Drugs

Two sample pools, containing a low and high concentration of CKMB were used. These sample pools were divided into an appropriate number of aliquots. One aliquot was not spiked with the drugs and was used as the reference sample for CKMB concentration. The CKMB concentration in the sample was determined with n = 3 measurements on a **cobas c** 501 analyzer.

The other sample aliquots, with either the high or low CKMB concentrations, were spiked with the respective amount of drug. The CKMB concentration of the spiked aliquots were determined in triplicate and the mean of the triplicate determinations was compared to the CKMB concentration determined for the reference aliquot (mean of n=3).

No interference was found at therapeutic concentrations using common drug panels with the exceptions of Cyanokit (Hydroxocobalamin) and Cefoxitin which interfere with the test.

4.6. Method Comparison to Predicate

A total of 105 human serum samples were tested in singlicate with the CK-MB assay on **cobas c** 501 and on the predicate device. 4 samples were spiked with CK MB rec human. The results

were calculated using Passing/Bablok regression.

$y = 0.977x + 1.12$

$t = 0.968$

4.7. Matrix Comparison - Anticoagulants

The effect of the presence of anticoagulants on analyte recovery was determined by method comparison, obtained from samples drawn into serum and different types of plasma collection tubes (K2 EDTA, K3 EDTA, Li Heparin, and Gel Separation). For Li Heparin 31 tubes, for K2 EDTA 30 tubes, for K3 EDTA 31 tubes and 31 gel Separation tubes were collected and filled completely.

Method comparison was executed by using the serum data as the reference. Slope, Intercept and Correlation were calculated.

Table 7: Matrix Comparison Results

Anticoagulant	Regression
Serum vs. Serum Gel Separation	y = 0.996x + 0.804, r = 1.00
Serum vs. Li-heparin	y = 1.00x – 0.616, r = 0.999
Serum vs. K2-EDTA	y = 1.00x – 0.717, r = 0.999
Serum vs. K3-EDTA	y = 0.995x - 0.062, r = 1.00

5. CLINICAL PERFORMANCE EVALUATION

Not applicable.

6. ADDITIONAL INFORMATION

6.1. Other Devices Marketed With This Assay

The Creatine Kinase-MB assay continues to use:

- Calibrator f.a.s. CK-MB
- PreciControl ClinChem Multi 1 and 2
- Diluent NaCl 9%

There have been no changes to these items marketed with the new Creatine Kinase-MB assay.

7. CONCLUSIONS

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