December 16, 2022

Siemens Healthcare Diagnostics Products GmbH
Martina Pfeiff
Regulatory Affairs Manager
Emil-von-Behring Str. 76
Marburg, 35041 Germany

Re: K212559
Trade/Device Name: CardioPhase® hsCRP
Regulation Number: 21 CFR 866.5270
Regulation Name: C-reactive protein immunological test system
Regulatory Class: Class II
Product Code: NQD
Dated: June 22, 2022
Received: June 23, 2022

Dear Martina Pfeiff:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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 Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see

https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Paula Caposino -S
Digitally signed by Paula Caposino -S
Date: 2022.12.16 10:44:12 -05'00'

Paula Caposino, Ph.D.
Acting Deputy Director
Division of Chemistry
and Toxicology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*

k212559

Device Name
CardioPhase® hsCRP

Indications for Use *(Describe)*

CardioPhase® hsCRP is an in-vitro diagnostic reagent for the quantitative determination of C-reactive protein (CRP) in human serum, and heparin and EDTA plasma by means of particle enhanced immunonephelometry using the BN II and BN ProSpec® System. In acute phase response, increased levels of a number of plasma proteins, including C-reactive protein, is observed. Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. High sensitivity CRP (hsCRP) measurements may be used as an independent risk marker for the identification of individuals at risk for future cardiovascular disease. Measurements of hsCRP, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, may be useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndromes.

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 per 21 CFR 807.92
Type of 510(k): Special 510(k)

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of the Safe Medical Device Act of 1990 and 21 CFR 807.92.

The assigned 510(k) number is: k212559

1. Submitter

Siemens Healthcare Diagnostics Products GmbH
Emil-von-Behring-Str. 76
35041 Marburg, Germany

Contact Person :	Martina Pfeiff
Email :	martina.pfeiff@siemens-healthineers.com
Phone:	+49 (174) 3319336
Fax:	+49 (6421) 394977
Date of Preparation:	June 23, 2022

2. Device Information

Proprietary Name:	***CardioPhase***® ***hs***CRP
Common or Usual Name:	C-reactive protein immunological test system
Product Code:	NQD
Classification Name:	system, test, C-Reactive Protein per 21CFR 866.5270
Regulatory Class:	II
510(k) Review Panel:	Immunology (82)

3. Legally Marketed Unmodified / Predicate Devices

Cleared for use on Siemens' BN Systems under K033908 on January 22, 2004 as an *in-vitro* diagnostic reagent for the quantitative determination of C-reactive protein (CRP) in human serum, and heparin and EDTA plasma by means of particle enhanced immunonephelometry using the BN Systems.

Trade Name	Common/Usual Name	Classification	Product Code	Panel	FDA clearance
CardioPhase ***hs***CRP	C-reactive protein immunological test system	Class II per 21CFR 866.5270	NQD	Immunology (82)	K964527* K991385 K033908

* Clearance of N Rheumatology Standard SL (calibrator used with above mentioned reagent)

4. Device Description / Test Principle

The ***Cardio***Phase ***hs***CRP assay is an *in vitro* diagnostic reagent for the quantitative determination C-reactive protein, in human serum, and heparinized and EDTA plasma by means of particle-enhanced immunoassay determination.

Polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by comparison with a standard of known concentration.

5. Intended Use / Indications for Use

CardioPhase ***hs***CRP assay

CardioPhase ***hs***CRP is an *in-vitro* diagnostic reagent for the quantitative determination of C-reactive protein (CRP) in human serum, and heparin and EDTA plasma by means of particle enhanced immunonephelometry using the BN II and BN ProSpec System. In acute phase response, increased levels of a number of plasma proteins, including C-reactive protein, is observed. Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. High sensitivity CRP (hsCRP) measurements may be used as an independent risk marker for the identification of individuals at risk for future cardiovascular disease. Measurements of hsCRP, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, may be useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndromes.

CardioPhase ***hs***CRP consists of a suspension of polystyrene particles coated with mouse monoclonal antibodies (< 0.016 g/L) to CRP.

N Rheumatology Standard SL

N Rheumatology Standard SL is used for the establishment of reference curves for the immunonephelometric determination of C-reactive protein on the BN II and BN ProSpec Systems. This calibrator consists of a mixture of human sera and elevated concentrations of CRP.

6. Special Conditions for Use Statements

For prescription use only.

AHA/CDC Expert Panel Recommendations:

hsCRP levels should not be substituted for assessment of traditional cardiovascular risk factors. Application of management guidelines for acute coronary syndromes should not be dependent on hsCRP levels.
In patients with stable coronary disease or acute coronary syndromes, hsCRP measurement may be useful as an independent marker of prognosis.
When using the assay for risk assessment, patients with persistently unexplained, marked elevation of hsCRP (> 10 mg/L) after repeated testing should be evaluated for non-cardiovascular etiologies.
The expert panel recommends against screening of the entire adult population for hsCRP as a public health measure.
Patients with evidence of active infection, systemic inflammatory processes or trauma should not be tested for cardiovascular disease risk assessment until these conditions have abated.

Application of secondary prevention measures should not depend on hsCRP determination, but rather an array of risk factors (global risk assessment).
Serial measurements of CRP should not be used to monitor effects of treatment.
Two separate CRP measurements (optimally two weeks apart) should be obtained before performing risk assessment, due to within-subject CRP variability.
Measurement of hsCRP is an independent marker of risk.

hsCRP levels may be useful in motivating patients to improve lifestyle behaviors.

7. Special instrument requirements:

BN II System (K943997)
BN ProSpec System(K001647)
BN Systems (nephelometry)

8. Technological characteristics

Similarities and Differences to the predicate:

The following is a table with a comparison of the similarities and differences between the proposed ERM-DA474/IFCC standardized ***Cardio***Phase ***hs***CRP assay to the predicate device ERM-DA470 standardized ***Cardio***Phase ***hs***CRP assay.

Table 8.-1: Similarities and Differences between proposed ERM-DA474/IFCC standardized and predicate ERM-DA470 standardized *Cardio*Phase *hs*CRP

	Predicate **Siemens Healthcare** ***Cardio*Phase *hs*CRP** ERM-DA470 standardized (K033908)	**Proposed Device** **Siemens Healthcare** ***Cardio*Phase *hs*CRP** ERM-DA474/IFCC standardized
Indications for Use	cardiac risk assessment and injury/inflammation	Same
Sample Type	Human serum, heparin and EDTA plasma	Same
Reagent Packaging	3 x 1 mL	Same
Units	mg/L	Same
Detection Method	Nephelometry	Same
Measurement	Quantitative	Same
Detection Antibody	Mouse monoclonal antibodies	Same
Reagent Composition	Polystyrene particles coated with monoclonal antibodies	Same
Calibrator	N Rheumatology Standard SL	Same
Traceability/Standardization	ERM-DA470	ERM-DA474/IFCC
Calibrator Levels	One level	Same
Analytical Measuring Range	CRP sensitive (CRP2) = 0.16 – 10 mg/L CRP (CRP1)= 3.1 – 200 mg/L	CRP sensitive (CRP2) = 0.16 – 10 mg/L CRP (CRP1)= 3.1 – 100 mg/L
Expected Values	Healthy Individuals ≤ 3 mg/L Cardiac Risk Stratification according to AHA/CDC Scientific Statement: Relative Risk hsCRP (mg/L) Low < 1.0 Average 1.0 – 3.0 High > 3.0	Same

The differences between the predicate device and proposed device do not result in a change to the intended use, the indications for use, or to safety and efficacy when used according to the product labeling.

9. Summary of Design Control Activities

A risk analysis was performed with risks identified. Mitigation of risk to acceptable levels was achieved through verification activities summarized below.

9.1 Risk Analysis

Risk analysis was performed according to the ISO14971:2019 standard, Medical Devices – Application of Risk Management to Medical Devices. The change to the standard reference material for the ***Cardio***Phase ***hs***CRP assay is the only change made to the test system. The reagents, packaging and instruments used for analysis remain unchanged. The labeling of the package insert for N Rheumatology Standard SL was updated including the reference to the new reference material ERM-DA474.

Each difference was analyzed, and its effect identified. Severity and probability were estimated by risk class. Risks were mitigated to the degree acceptable.

9.2. Verification Activities

Based on the results of the risk analysis, verification activities were identified, pertinent studies were determined and acceptance criteria established. The following studies were necessary to determine substantial equivalence:

9.3. Performance Studies

9.3.1 Detection Capabilities

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined according to the CLSI document EP17-A2:2012, *Evaluation of Detection Capability for Clinical* CLSI *Laboratory Measurement Procedures; Approved Guideline—Second Edition*. The LoB and LoD estimates were evaluated separately for each reagent lot on each BN System and the reagent lot and analyzer combination yielding the highest value was used for the LoB, LoD and LoQ claims.

The LoB study was performed with five (5) independent analyte-free samples. The LoB study was carried out with one (1) BN ProSpec System, one (1) BNII System, three (3) different reagent lots, one (1) calibrator lot, five (5) analyte-free samples, one (1) single determination of five (5) individual aliquots of each sample on three (3) days and with one (1) trained operator. This protocol results in 75 measurements per reagent lot, a total of 450 measurements (including the two workflows) on each of the two (2) analyzers resulting in 900 measurements overall.
All results measured on blank samples for the LoB study yielded results below the respective LoQ.

To determine the limit of the detection (LoD) and Limit of Quantitation (LoQ), serum samples with concentrations ranging from approximately 0.05 mg/L to 0.26 mg/L CRP were prepared. Five replicates of six patient samples were run once per day for five days using three hsCRP Reagent lots on one BNProSpec and one BN II totaling 1080 determinations. The Limit of Detection (LoD) was calculated parametrically following the recommendations in the CLSI guideline. The LoD is greater than Limit of Blank and equal or below Limit of Quantitation

The Limit of Quantitation (LoQ) was calculated using the data generated for the LoD study and was based on an imprecision goal of less than 20% CV. The LoQ was set to 0.094 mg/L based on the sample/instrument/reagent lot combination with the highest imprecision observed in the study (<11%CV).

9.3.2 Linearity

A linearity study was performed according to CLSI EP06-Ed2, *Evaluation of the Linearity of Quantitative Measurement Procedures: A statistical Approach*.
A high CRP serum pool was mixed with different proportions of a low serum pool to generate 13 concentrations covering the measuring ranges of CRP sensitive - CRP2 (0,16 -10 mg/L) and CRP - CRP1 (3.1-100 mg/L with each level tested in four-fold determination on BN ProSpec and BN II System.

For result calculation the deviation between the mean measured value and the predicted value of a weighted linear regression was compared to the predefined acceptance criteria.

The following linear ranges were found confirming the upper end of the measuring ranges:

CRP sensitive (CRP2):	0.151 – 10.89 mg/L (measuring range:0.16-10 mg/L)
CRP (CRP1):	1.478 – 224 mg/L (measuring range: 3.1-100 mg/L)

9.3.3 Method Comparison

A method comparison using native samples in the range of 0.27 and 11.90 mg/L between the CardioPhase® hsCRP assay (cleared in 2003 under premarket clearance K033908; standardized to ERM-DA470, x-axis) and candidate assay (standardized to ERM-DA474/IFCC, y-axis) produced a predicted bias of 6.9 % at 1 mg/L, and 7.5 % at 3 mg/L for CRP2 and using native samples in the range of 3.87 and 61.40 mg/L between the CardioPhase® hsCRP assay (cleared in 2003 under premarket clearance K033908; standardized to ERM-DA470, x-axis) and candidate assay (standardized to ERM-DA474/IFCC, y-axis) produced a predicted bias of 8.17% at 10 mg/L for CRP1.

9.4 Matrix Comparison

Siemens conducted a study to confirm equivalence for serum and EDTA plasma and for serum and lithium heparin plasma for the ERM-DA474/IFCC standardized ***Cardio***Phase ***hs***CRP assay.For each sample type, a total of 60 native samples spanning the measuring range were evaluated. The data was collected using one instrument (BNProSpec and BNII System), and 3 lots of reagent. A Passing-Bablok linear regression analysis was performed comparing the material used in the studies (serum) to EDTA and lithium-heparinized plasma.

The results for one reagent lot are shown in the tables below.

Table 9.4.1: Results matrix comparison-CRP (CRP1)

Application	N	Slope (95% CI)	Intercept (95% CI)	Pearson Correlation Coefficient (r)
CRP1 with ***Cardio***Phase ***hs***CRP on BNPS System Serum vs. EDTA Plasma	60	0.972 (0.954 to 0.992)	0.091 (-0.218 to 0.281)	0.998
CRP1 with ***Cardio***Phase ***hs***CRP on BN II System Serum vs. EDTA Plasma	60	0.986 (0.947 to 1.012)	0.068 (-0.186 to 0.276)	0.997
CRP1 with ***Cardio***Phase ***hs***CRP on BNProSpec System Serum vs. Heparin Plasma	60	0.989 (0.963 to 1.013)	-0.097 (-0.470 to 0.109)	0.995
CRP1 with ***Cardio***Phase ***hs***CRP on BN II System Serum vs. Heparin Plasma	60	1.018 (0.989 to 1.045)	-0.118 (-0.363 to 0.044)	0.995

Table 9.4.1: Results matrix comparison-CRP sensitive(CRP2)

Application	N	Slope (95% CI)	Intercept (95% CI)	Pearson Correlation Coefficient (r)
CRP2 with ***Cardio***Phase ***hs***CRP on BNPS System Serum vs. EDTA Plasma	74	1.056 (1.009 to 1.103)	-0.014 (-0.132 to 0.070)	0.974
CRP2 with ***Cardio***Phase ***hs***CRP on BN II System Serum vs. EDTA Plasma	74	1.061 (1.016 to 1.118)	-0.009 (-0.118 to 0.072)	0.970
CRP2 with ***Cardio***Phase ***hs***CRP on BNProSpec System Serum vs. Heparin Plasma	74	0.967 (0.931 to 1.002)	-0.035 (-0.136 to 0.062)	0.983
CRP2 with ***Cardio***Phase ***hs***CRP on BN II System Serum vs. Heparin Plasma	74	0.962 (0.913 to 0.997)	-0.024 (-0.123 to 0.054)	0.979

The results of the matrix comparison study confirm equivalence for serum and EDTA-plasma and for serum and lithium heparin plasma for the ERM-DA474/IFCC standardized ***Cardio***Phase ***hs***CRP assay.

9.5 Traceability

The calibration of the assay is traceable to the IFCC European Reference Material ERM-DA474/IFCC, certified for C-reactive protein measurements.

9.5.1 Calibrator Traceability

N Rheumatology Standard SL is traceable to Siemens internal Master Calibrator which is directly traceable to ERM-DA474/IFCC.

10. Comments on Substantial Equivalency

The reagents for the proposed devices and the cleared devices are identical in composition, labeling and packaging. Comparative testing was performed, and the results obtained demonstrate substantial equivalent performance.

The use of the reagent with N Rheumatology Standard SL traceable to ERM-DA474/IFCC does not affect safety and efficacy when used according to the product labeling.

11. Conclusion

The modified device, ***Cardio***Phase ***hs***CRP traceable to ERM-DA474/IFCC, is substantially equivalent to the predicate device, ***Cardio***Phase ***hs***CRP traceable to ERM-DA470 based on intended use design, and basic scientific principle and performance.

Results from the risk analysis and design control activities with comparative testing support a substantial equivalence decision.