November 27, 2023

Siemens Healthcare Diagnostic Products GmbH
Petra Dissmann
Regulatory Affairs Manager
Emil-von Behring Strasse 76
Marburg, Hessen 3504
Germany

Re: K232624
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: DCN, NQD
Dated: August 29, 2023
Received: August 29, 2023

Dear Petra Dissmann:

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 (the 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 available 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

(https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 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,

Ying Mao -S

Ying Mao, Ph.D.
Branch Chief
Division of Immunology and Hematology 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)*
K232624

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.

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K232624 (CardioPhase® hsCRP) - 510(k) Summary

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of 21 CFR §807.92, the Safe Medical Act of 1990, and follows the FDA guidance 'The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]', issued July 28, 2014.

1. Applicant

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Phone:	+ 49 172 369 245 9
Date Prepared:	November 22, 2023

2. Device

Name of Device:	CardioPhase® hsCRP
Regulation Number:	21 CFR 866.5270
Regulation Description:	C-reactive protein immunological test system
Product Code:	NQD
Device Classification Name:	Cardiac C-Reactive Protein, Antigen, Antiserum, And Control
Regulatory Class:	Class II
510(k) Review Panel	Immunology (82)

3. Predicate Device

Name of Device / 510(k):	RCRP Flex® reagent cartridge / K221119
Regulation Number:	21 CFR 866.5270
Regulation Description:	C-reactive protein immunological test system
Product Code:	DCN
Device Classification Name:	System, test, C-reactive protein
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

4. Device Description / Test Principle

The CardioPhase hsCRP assay is an in-vitro diagnostic reagent for the quantitative determination of C-reactive protein (CRP) in human serum, and heparinized and EDTA plasma by means of particle-enhanced immunoassay determination. The assay is traceable to the international standard ERM-DA474/IFCC.

N Rheumatology Standard SL (cleared under K964527) 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.

The CardioPhase hsCRP reagent is a suspension of polystyrene (Latex) particles to which mouse monoclonal anti-human CRP antibodies (< 0.016 g/L) have been attached by covalent bonding. The reagent is a ready-to-use liquid containing preservatives.

There are two product variants available. One variant (REF OQIY13) contains 3 x 2 mL vials / box, and the other variant (REF OQIY21) contains 5 x 5 mL vials / box.

The assay's 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 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.

6. Special Conditions for Use Statements

For prescription use only.

<u>AHA/CDC Expert Panel Recommendations:</u>

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)

Both analyzers together are summarized as BN Systems (nephelometry)

8. Comparison of Technological Characteristics with the Predicate Device

The following table presents a comparison of the similarities and differences between the proposed device CardioPhase hsCRP and the predicate device RCRP Flex reagent cartridge (K221119).

Similarities and differences between the predicate and the proposed device		
Item	**<u>Predicate Device</u> Siemens Healthineers RCRP Flex reagent cartridge (K221119)**	**<u>Proposed Device</u> Siemens Healthineers CardioPhase hsCRP**
Regulation Number **Regulation Description** **Regulatory Class** **510(k) Review Panel**	21 CFR 866.5270 C-reactive protein immunological test system Class II Immunology (82)	Same Same Same Same
Product Code **Device Classification Name**	DCN System, test, c-reactive protein	NQD Cardiac C-Reactive Protein, Antigen, Antiserum, And Control

Similarities and differences between the predicate and the proposed device		
Item	**<u>Predicate Device</u> Siemens Healthineers RCRP Flex reagent cartridge (K221119)**	**<u>Proposed Device</u> Siemens Healthineers CardioPhase hsCRP**
Indications for Use / Intended Use	The C-Reactive Protein Extended Range (RCRP) method used on the Dimension® clinical chemistry system is an in vitro diagnostic test intended for the quantitative determination of CRP in human serum and plasma (lithium heparin). Measurement of C-Reactive Protein is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases.	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.

Similarities and differences between the predicate and the proposed device		
Item	**<u>Predicate Device</u> Siemens Healthineers RCRP Flex reagent cartridge (K221119)**	**<u>Proposed Device</u> Siemens Healthineers CardioPhase hsCRP**
Sample Type	Human serum, plasma (lithium heparin)	Human serum, plasma (heparin and EDTA)
Analyte	C-reactive Protein (CRP)	Same
Units	mg/L	Same
Measurement	Quantitative	Same
Test Principle biochemical principle of reagent	Synthetic particles coated with antibody to C-Reactive Protein (AbPR) aggregate in the presence of C-Reactive Protein in the sample. The increase in turbidity which accompanies aggregation is proportional to the C-Reactive Protein concentration.	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.
Test Principle analyzer measuring principle **(wavelength)**	Particle-enhanced Immuno-turbidimetry (PETIA) 340 nm	Particle-enhanced Immuno-nephelometry 840 nm
Reagent Composition	Synthetic particles coated with antibody to C-Reactive Protein (goat), preservative, buffer	Polystyrene particles coated with monoclonal antibodies specific to human CRP (mouse), preservative, buffer
Form	Liquid suspension	Same
Calibrator	Dimension Revised C-Reactive Protein Calibrator	N Rheumatology Standard SL
Traceability/Standardization	Traceable to ERM-DA474/IFCC	Same
Calibrator Levels	Five levels (five individual vials)	One level (one standard diluted to seven concentration levels)
Storage	Until expiration date (indicated on the box label) when stored at 2 – 8°C	same

Similarities and differences between the predicate and the proposed device		
Item	**<u>Predicate Device</u> Siemens Healthineers RCRP Flex reagent cartridge (K221119)**	**<u>Proposed Device</u> Siemens Healthineers CardioPhase hsCRP**
Sample stability	Fresh samples, max. 8 h at room temperature 72 h at 4°C 6 months frozen at -20°C	Fresh samples (when diluted stable for 4 h) 8 days at 2 – 8°C 8 months frozen at -20°C
Antigen excess	unknown	Up to: CRP1: 1347.9 mg/L CRP2: 1302.2 mg/L
Analytical Measuring Range	5.0 to 250.0 mg/L	0.16 to 10 mg/L (with workflow CRP2) 3.1 to 200 mg/L (with workflow CRP1)
Expected Values	< 5.0 mg/L	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 to 3.0 High > 3.0
Linearity	5.0 - 250.0 mg/L	CRP (CRP1 workflow) 1.478 - 224 mg/L hsCRP (CRP2 workflow) 0.151 - 10.890 mg/L
Precision	Serum sample range from 6.8 mg/L till 233.4 mg/L Repeatability (within-run) CV from 0.8% till 1.7% Within-Lab CV from 1.1% till 2.6%	Serum and control sample range from 0.69 mg/L till 179 mg/L Repeatability (within-run) CV from 2.1% till 4.6% Within-Lab CV from 2.2% till 5.8%

Similarities and differences between the predicate and the proposed device		
Item	**<u>Predicate Device</u> Siemens Healthineers RCRP Flex reagent cartridge (K221119)**	**<u>Proposed Device</u> Siemens Healthineers CardioPhase hsCRP**
Interference of bilirubin, hemoglobin, triglycerides	No interference bias was detected for tested concentration: Hemoglobin (hemolysate) [500 mg/dL] 5.0 g/L Bilirubin (unconjugated) [40 mg/dL] 684 µmol/L Lipemia (Intralipid) [250 mg/dL] 2.5 g/L Lipemia (Trig Fraction) [750 mg/dL] 7.5 g/L	No interference was detected in serum for concentrations of free hemoglobin up to 10 g/L, bilirubin up to 0.6 g/L, and triglycerides up to 16 g/L.

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.

The re-extension of the measuring range for the CardioPhase hsCRP assay is the only change made to the test system. The reagent, packaging and instruments used for analysis remain unchanged.

9.2. Verification Activities

Based on the results of the risk analysis, a method comparison was identified as verification activity and acceptance criteria established.

9.3. Performance Studies

A method comparison study was performed for the extension of the CRP1 workflow measuring range of CardioPhase hsCRP cleared under K212559.

9.3.1 Method Comparison

A method comparison study designed according to CLSI document EP09c '*Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition*' was conducted at the company site in Marburg, Germany. Native serum samples were measured on both the predicate device (RCRP Flex® reagent cartridge on the Dimension clinical chemistry system, cleared under K221119) as well as on the proposed device (CardioPhase hsCRP assay on a BN System). Both devices are traceable to ERM-DA474/IFCC. The intended measuring interval of the CardioPhase hsCRP workflow CRP1 on the BN Systems (3.1 to 200 mg/L) was well covered. Three (3) lots of CardioPhase hsCRP were compared to the predicate device. Results were compared by Passing-Bablok regression analysis. Results from each lot of lot of CardioPhase hsCRP met the predefined acceptance criteria. The

following summary of Passing-Bablok regression shows that the proposed and predicate devices provide equivalent results. The observed maximum predicted bias for CRP concentrations of 10, 100, 150 and 200 mg/L was 5.2% (relative).

Method Comparison Results **Predicate Device:** RCRP Flex® reagent cartridge on the Dimension clinical chemistry system **Proposed Device:** CardioPhase hsCRP assay on a BN System		
Lot 1 CardioPhase hsCRP	**Lot 2 CardioPhase hsCRP**	**Lot 3 CardioPhase hsCRP**
N = 119 Range: 5.523 – 197.746 mg/L y = 0.959x + 0.932 mg/L r = 0.994 (r^2 = 0.989)	N = 116 Range: 5.378 – 199.150 mg/L y = 0.955x + 0.584 mg/L r = 0.996 (r^2 = 0.991)	N = 113 Range: 5.501 – 199.503 mg/L y = 1.032x - 0.070 mg/L r = 0.994 (r^2 = 0.989)

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 Siemens Healthcare Diagnostics Products GmbH believes that the data presented in this 510(k) premarket notification as well as the descriptions of similarities and differences support a decision of substantial equivalence between the CardioPhase hsCRP assay and the predicate device, RCRP Flex reagent cartridge (K221119). These two medical devices have equivalent intended uses, technology and performance specifications. Therefore, a premarket clearance is supported based on the performance testing data provided in this submission.

11. Conclusion

The presented method comparison supports FDA’s substantial equivalence decision for the upper measuring range of up to 200 mg/L for the CRP1 workflow of the CardioPhase hsCRP assay on the BN systems compared to the predicate device, RCRP Flex reagent cartridge on the Dimension analyzer (K221119). The data submitted for this premarket notification demonstrates that the device raises no concerns regarding safety and effectiveness.