March 17, 2023

Siemens Healthcare Diagnostics Inc.
Ian Thompson
Regulatory Affairs Professional
511 Benedict Avenue
Tarrytown, New York 10591

Re: K221119
Trade/Device Name: RCRP Flex reagent cartridge
Regulation Number: 21 CFR 866.5270
Regulation Name: C-Reactive Protein Immunological Test System
Regulatory Class: Class II
Product Code: DCN
Dated: January 20, 2023
Received: January 23, 2023

Dear Ian Thompson:

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,

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)*
K221119

Device Name
RCRP Flex® reagent cartridge

Indications for Use *(Describe)*
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.

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

The assigned 510(k) Number is: K221119

1. Date Prepared

January 20, 2023

2. Applicant Information

Contact:	Ian Thompson Regulatory Affairs Professional
Address:	511 Benedict Avenue Tarrytown, NY 10591-5097
Email:	ian_thompson@siemens-healthineers.com

3. Regulatory Information

Dimension RCRP Flex® reagent cartridge assay

Trade Name:	RCRP Flex® reagent cartridge
Common Name:	System, Test, C-Reactive Protein
Classification Name:	C-reactive protein immunological test system
FDA Classification:	Class II
Review Panel:	Immunology
Product Code:	DCN
Regulation Number:	21 CFR 866.5270

4. Predicate Device Information

Predicate Device Name: RCRP Flex® reagent cartridge assay

510(k) Number: K003419

5. Intended Use / Indications For 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.

Special Conditions for Use Statement(s): For Prescription Use Only.

6. Device Description

The RCRP method is based on a particle enhanced turbidimetric immunoassay (PETIA) technique.

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.

7. Purpose of Submission

The purpose of this submission is a special 510(k) premarket notification for a modified device: RCRP Flex® reagent cartridge assay. This device was modified by updating the traceability from the IFCC CRM 470 reference material to the ERM-DA474/IFCC reference material.

A Special 510(k) Premarket Notification is the requested pathway because of the following:

- The change is to the manufacturer's own legally marketed device.
- There is no change to the intended use or indications for use.
- There is no change in the fundamental scientific technology.
- There is no change to the principle of operation.
- There is no change to the formulation.
- There is no change to the instrument parameters related to sample volume, reagent volume, mix speed, wavelengths, or read times.

8. Comparison of Candidate Device and Predicate Device

The table below describes the similarities and difference between the modified RCRP Flex reagent cartridge assay (Candidate Device) and RCRP Flex reagent cartridge assay (Predicate Device cleared under K003419). The Candidate Device and Predicate Device employ the same prepackaged reagents for use on an automated test system. The Intended Use / Indications for Use, assay principle, and reagent formulations are the same.

The Instructions for Use (IFU)/Package Insert for the Dimension Revised C-Reactive Protein Calibrator (RCRP CAL) was updated for this change.

The method comparison study between the Candidate Device and the Predicate Device demonstrated acceptable correlation.

Feature	**Candidate Device**	**Predicate Device**
	RCRP Flex reagent cartridge	**RCRP Flex reagent cartridge**
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).	Same
Indications for Use	Measurement of C-Reactive Protein is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases.	Same

Feature	Candidate Device	Predicate Device
	RCRP Flex reagent cartridge	RCRP Flex reagent cartridge
Sample Type	serum and plasma (lithium heparin)	Same
Units of Measure	mg/L	Same
Analytical Measurement Range	5.0 – 250.0 mg/L	0.5 – 250.0 mg/L
Expected Values	< 5.0 mg/L	3 mg/L
Assay Principle	Particle enhanced turbidimetric immunoassay (PETIA)	Same
Standardization	ERM-DA474/IFCC	IFCC CRM 470
Calibrator Levels	Five levels	Same
Calibrator	Dimension Revised C-Reactive Protein Calibrator	Same

9. Standard/Guidance Document References

The following recognized standards from Clinical Laboratory Standards Institute (CLSI) were used as a basis of the study procedures described in this submission:

Evaluation Measurement Procedure Comparison and Bias Estimation Using Patient Samples (CLSI EP09c-ED3).
Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline–Second Edition (EP17-A2).
Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP06-ED2).
Interference Testing in Clinical Chemistry: Approved Guidelines (CLSI EP07-ED3).
Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory (CLSI EP28-A3c).
Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline–Third Edition (CLSI EP05-A3).
User Verification of Precision and Estimation of Bias; Approved Guideline–Third Edition (CLSI EP15-A3).

10. Summary of Design Control Activities

A risk analysis was performed to evaluate the risks associated with the modification.

10.1 Risk Analysis

Risk analysis was conducted according to ISO 14971:2012 standard, *Medical Devices – Application of Risk Management to Medical Devices*, to assess the impact of the modification.

This risk analysis supports that the modification did not introduce any new risk to the performance of the modified RCRP Flex reagent cartridge assay.

10.2 Verification Activities

Based on the risks analysis, verification testing was performed for updating the traceability from the IFCC CRM 470 reference material to the ERM-DA474/IFCC reference material. Method comparison, linearity, functional sensitivity/LoQ, and additional studies were conducted.

Method Comparison – Modified RCRP assay vs Predicate RCRP assay

Method comparison study was conducted in accordance with CLSI EP09-A3. Individual human native serum samples were tested on the Dimension RXL system. The serum samples were obtained from specimen vendors. The modified RCRP Flex reagent cartridge assay was calibrated with calibrator traceable to ERM-DA474/IFCC reference material. The predicate RCRP Flex reagent cartridge assay was calibrated with the calibrator traceable to IFCC CRM 470 reference material. A single replicate was processed for each sample on calibration conditions. Eighteen (18) out of 132 samples tested were within the range of 7.5 and 12.5 mg/L (14% of total samples). The slope, y-intercept, and correlation coefficient (r) results were generated using Deming regression. The correlation between the modified assay and the predicate assay are summarized below in Table 1 and Table 2.

Table 1. Method Comparison Results Summary

Modified Method (y)	Predicate Method (x)	Regression Equation	Sample Interval	N[a]	r[b]
RCRP with Calibrator Traceable to ERM-DA474/IFCC Reference Material	RCRP with Calibrator Traceable to IFCC CRM 470 Reference Material	y = 0.99x – 0.5 mg/L	5.0 to 247.6 mg/L	132	1.000

[a] Number of samples tested.
[b] Correlation coefficient.

Table 2. Method Comparison Requirements and Results Summary

Attribute	Acceptance Criteria	Observed	Pass/Fail
Slope	1.00 ± 0.1	0.99	Pass
y-intercept	0.0 ± 2.0 mg/L	-0.5 mg/L	Pass
Correlation Coefficient (r)	≥ 0.9600	1.000	Pass

Method Comparison – RCRP assay on Dimension RXL system vs N High Sensitivity CRP on the BN™ System

For the change in the analytical measurement range (AMR) from [0.5 – 250.0 mg/L] 0.05 – 25.00 mg/dL to [5.0 – 250.0 mg/L] 0.50 – 25.00 mg/dL, the historical IFU data was re-analyzed and the IFU was updated with the summary of the results for the method comparison of the candidate RCRP assay on Dimension RXL clinical chemistry system versus the predicate N High Sensitivity CRP on the BN™ System.

The correlation between the candidate and the predicate are summarized below in Table 3 and Table 4.

Table 3. Method Comparison Re-Analyzed Results Summary					
Candidate Method (y)	**Predicate Method (x)**	**Regression Equation**	**Sample Interval**	**N[a]**	**r[b]**
RCRP Dimension RXL clinical chemistry system	N High Sensitivity CRP on the BN™ System	y = 0.95x – 1.6 mg/L	5.3 to 241.3 mg/L	171	0.997
		y = 0.86x – 0.2 mg/L	5.3 to 20.2 mg/L	39	0.986

Table 4. Method Comparison Requirements and Re-Analyzed Results Summary			
Attribute	**Acceptance Criteria**	**Observed**	**Pass/Fail**
Slope	1.00 ± 0.10	0.95	Pass
y-intercept	0.0 ± 2.0 mg/L	-1.6 mg/L	Pass
Correlation Coefficient (r)	≥ 0.9600	0.997	Pass

Linearity

Linearity study was conducted in accordance with CLSI EP06-ED2.

The modified RCRP Flex reagent cartridge assay is linear for the analytical measurement range of 5.0 – 250.0 mg/L.

Detection Capability

Verification of the existing Analytical Sensitivity and Functional Sensitivity in the Instructions for Use (IFU/Pacakage Insert) was replaced with conducting Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies.

The Limit of Blank (LoB) corresponds to the highest measurement result that is likely to be observed for a blank sample. The assay is designed to have an LoB ≤ Limit of Detection (LoD).

The LoD corresponds to the lowest concentration of CRP that can be detected with a probability of 95%. The assay is designed to have an LoD ≤ the LoQ.

The LoQ corresponds to the lowest concentration of CRP in a sample at which the within-laboratory precision is ≤ 20% CV. The assay is designed to have an LoQ ≤ [5.0 mg/L] 0.50 mg/dL.

Detection capability was determined in accordance with CLSI Document EP17-A2.

The results support the following claims:

Specimen Type	Detection Capability	Result
Serum and Lithium Heparin Plasma	LoB	0.6 mg/L (0.06 mg/dL)
	LoD	1.0 mg/L (0.10 mg/dL)
	LoQ	5.0 mg/L (0.50 mg/dL)

Precision

Precision was verified in accordance with CLSI Document EP05-A3. Samples at each level were analyzed N=10 replicates each day for 5 days. The following results were obtained:

Specimen Type	N[a]	Mean		Repeatability (Within-run)			Within-Lab (Total)		
				SD[b]		CV[c]	SD		CV
		mg/L	mg/dL	mg/L	mg/dL	(%)	mg/L	mg/dL	(%)
Serum 1	50	6.8	0.68	0.08	0.008	1.2	0.12	0.012	1.8
Serum 2	50	9.1	0.91	0.07	0.007	0.8	0.17	0.017	1.9
Serum 3	50	37.7	3.77	0.32	0.032	0.8	0.42	0.042	1.1
Serum 4	50	108.4	10.84	1.07	0.107	1.0	1.59	0.159	1.5
Serum 5	50	208.3	20.83	3.37	0.337	1.6	4.76	0.476	2.3
Serum 6	50	233.4	23.34	3.95	0.395	1.7	6.15	0.615	2.6

[a] Number of replicates tested.
[b] Standard deviation.
[c] Coefficient of variation.

Specimen Equivalency

Specimen equivalency was verified using the Deming regression model in accordance with CLSI EP09C-ED3. The following results were obtained:

Specimen (y)	Reference Specimen (x)	Regression Equation	Sample Interval	N[a]	r[b]
Lithium heparin plasma	Serum	y = 0.99x + 0.1 mg/L	5.2 to 243.2	73	1.00

[a] Number of samples tested.
[b] Correlation Coefficient.

Interference

For the change in the analytical measurement range (AMR) from [0.5 – 250.0 mg/L] 0.05 – 25.00 mg/dL to [5.0 – 250.0 mg/L] 0.50 – 25.00 mg/dL, the hemolysis, icterus, and lipemia (HIL) interference study was repeated using sample with CRP analyte level within the new range.

The modified assay was evaluated for interference from hemolysis, icterus and lipemia according to EP07-ED3. Bias defined as the difference between the control sample (does not contain interferent) and the test sample (contains the interferent), is shown in the table below. Bias exceeding 10% is considered “interference”.

Endogenous Substance Tested	Endogenous Substance Concentration	Analyte Concentration	Bias (%)
Hemoglobin (hemolysate)	[500 mg/dL] 5.0 g/L	[11.6 mg/L] 1.16 mg/dL	0%

Endogenous Substance Tested	Endogenous Substance Concentration	Analyte Concentration	Bias (%)
Bilirubin (Unconjugated)	[40 mg/dL] 684 µmol/L	[11.7 mg/L] 1.17 mg/dL	2%
Lipemia (Intralipid)	[250 mg/dL] 2.5 g/L	[11.8 mg/L] 1.18 mg/dL	-9%
Lipemia (Triglyceride Fraction)	[750 mg/dL] 7.5 g/L	[11.1 mg/L] 1.11 mg/dL	-7%

Expected Values

The reference interval was verified in accordance with CLSI EP28-A3c.

The reference interval was verified as < 5.0 mg/L.

11. Comments on Substantial Equivalency

The modified RCRP Flex reagent cartridge assay and the predicate RCRP Flex reagent cartridge assay are identical in composition, labeling and packaging. Verification testing results demonstrate equivalent performance.

12. Conclusion

Results from the risk analysis and design control activities with comparative testing support that the modified RCRP Flex reagent cartridge assay is substantially equivalent to the predicate RCRP Flex reagent cartridge assay (K003419).