Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K191993

B Applicant

Horiba ABX SAS

C Proprietary and Established Names

Yumizen C1200 CRP

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DCK	Class II	21 CFR 866.5270 - C-Reactive Protein Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

C-Reactive Protein (CRP)

C Type of Test:

Quantitative, immunoturbidimetric assay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
Yumizen C1200 CRP reagent is intended for use as a high sensitive assay for the quantitative in vitro diagnostic determination of the C-reactive protein in human serum and plasma based on an immunoturbidimetric assay. CRP is used to evaluate conditions thought to be associated with inflammation in otherwise healthy individuals.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:

Yumizen C1200 Clinical Chemistry Analyzer

IV Device/System Characteristics:

A Device Description:

The device consists of two reagents, 1 and 2, as follows:

Reagent 1: Buffer solution: glycine buffer solution
Reagent 2: Latex suspension: 0.20% w/v suspension of latex particles sensitized with anti-CRP antibodies (rabbit)

B Principle of Operation:

Immune complexes formed in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters measure the reduction of incidence light due to reflection, absorption or scatter. In this procedure, the measurement of the rate of decrease in light intensity transmitted (increase in absorbance) through particles suspended in solution is the result of complexes formed during the immunological reaction between the CRP of the patient sample and rabbit anti-CRP-antibodies coated on latex particles.

V Substantial Equivalence Information:

A Predicate Device Name(s):
VITROS Chemistry Products hsCRP Reagent

B Predicate 510(k) Number(s):
K160712

C Comparison with Predicate(s):

Device & Predicate Device(s):	K191993	K160712
Manufacturer	HORIBA ABX SAS	Ortho-Clinical Diagnostics, Inc.
Device Trade Name	**Yumizen C1200 CRP**	**Vitros Chemistry Products hsCRP Reagent**
General Device Characteristic Similarities		
Indications For Use	Quantitative determination of the C-reactive protein used to evaluate conditions thought to be associated with inflammation in otherwise healthy individuals.	Same
General Device Characteristic Differences		
Traceability	Traceable to IRMM/ERM-DA472/IFCC	Traceable to IRMM/ERM-DA474/IFCC

VI Standards/Guidance Documents Referenced:

CLSI Guidelines:

- CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures – Third Edition
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures – Second Edition
- CLSI EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach – First Edition
- CLSI EP28-A3, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory – Third Edition

FDA Guidances:

- Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s – 2005

- Refuse To Accept (RTA) Policy for 510(k) – Guidance for Industry and Food and Drug Administration Staff – Document issued on February 21, 2019

- Guidance for Industry and FDA Staff: eCopy Program for Medical Device Submissions – 2015

- Guidance for Industry and FDA Staff: Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays – Document issued on September 22, 2005

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Serum

Reproducibility was evaluated following the recommendations in CLSI EP05-A3 guideline using 3 analyzers and 3 reagent lots (one lot per analyzer). One internal control (Low CRP Control) and 4 serum samples covering the measuring range (low, medium, and high) were tested in duplicate for 20 days, 2 runs per day. The results of reproducibility studies are summarized in the tables below, where within-laboratory precision subsumes within-run, between-run, and between-day precision:

Sample	n	Mean mg/L	Within-Run		Between-Run	
			SD mg/L	CV (%)	SD mg/L	CV (%)
Low CRP Control	240	1.50	0.022	1.5	0.027	1.8
Sample 1	240	0.34	0.016	4.7	0.009	2.8
Sample 2	240	0.83	0.013	1.6	0.021	2.6
Sample 3	240	4.13	0.026	0.6	0.068	1.7
Sample 4	240	8.73	0.068	0.8	0.220	2.5

Sample	n	Mean mg/L	Between-Day		Within-Laboratory	
			SD mg/L	CV (%)	SD mg/L	CV (%)
Low CRP Control	240	1.50	0.028	1.9	0.045	3.0
Sample 1	240	0.34	0.008	2.3	0.020	5.9
Sample 2	240	0.83	0.007	0.9	0.026	3.1
Sample 3	240	4.13	0.071	1.7	0.102	2.5
Sample 4	240	8.73	0.104	1.2	0.253	2.9

Within-run precision in serum was assessed by testing 2 controls and 6 native serum specimens (sample low, mid, and high), 20 times each, in a single run for each sample. The results of within-run precision studies are summarized below.

Sample	n	Mean mg/L	Within-Run Precision	
			SD mg/L	CV (%)
Level 1 Control	20	1.10	0.04	3.29
Level 2 Control	20	2.15	0.05	2.27
Sample 1	20	0.32	0.01	4.50
Sample 2	20	0.48	0.02	4.62
Sample 3	20	1.11	0.03	2.37
Sample 4	20	5.55	0.05	0.85
Sample 5	20	8.08	0.10	1.24
Sample 6	20	9.24	0.08	0.90

Lithium Heparin Plasma

Within-run precision in lithium heparin plasma was assessed by testing 6 specimens (sample low, mid, and high), 20 times each, in a single run for each sample. The samples tested were native plasma samples. The results of within-run precision studies are summarized below.

Sample	n	Mean mg/L	Within-Run Precision	
			SD mg/L	CV (%)
Sample 1	20	0.35	0.01	2.17
Sample 2	20	0.51	0.01	2.11
Sample 3	20	1.25	0.01	1.00
Sample 4	20	4.75	0.11	2.27
Sample 5	20	7.77	0.10	1.31
Sample 6	20	9.31	0.06	0.69

2. Linearity:

A linearity study was performed following the recommendations in CLSI EP06-A. A high serum pool with a CRP concentration of 11.53 mg/L was prepared by spiking a patient serum pool with CRP. A commercially available low serum pool with a CRP concentration of 0.03 mg/L was used. The high serum pool was then diluted with the low serum pool to create 10 intermediate samples (for a total of 12) covering and spanning the measuring range. Each sample was tested in replicates of 3. Results of the polynomial analysis demonstrated that the assay is linear, i.e., no second- or third-order fit was significantly better than the linear fit.

Linear regression analysis produced a slope of 0.9794, an intercept of 0.1996, and an r^2 value of 0.9983.

3. Analytical Specificity/Interference:

Common endogenous substances were evaluated for potential interference with the candidate assay. The effect of these interferents was confirmed by dose-response testing at varying concentrations of the interfering substance.

Samples were tested at five concentrations of interferent including an interferent-free control, four replicates each, on serum samples representing normal (~1 mg/L) and high (~5 mg/L)

concentrations of CRP (except for Rheumatoid Factor, which was tested in two high-concentration samples, ~5 and ~9 mg/L).

At the following concentrations, the maximum observed % difference was ≤ ± 10%. The data provided supports the sponsor's claims that no interference was seen at the concentrations tested below:

- Hemoglobin – up to 500 mg/dL
- Triglycerides – up to 279 mg/dL
- Total Bilirubin – up to 27.61 mg/dL
- Direct Bilirubin – up to 30.41 mg/dL
- Acetylsalicylic Acid – up to 65.16 mg/dL
- Ascorbic Acid – up to 5.98 mg/dL
- Ibuprofen – up to 50.10 mg/dL
- Acetaminophen – up to 20 mg/dL
- Rheumatoid Factor – up to 400 IU/mL when measured at ~5 mg/L and ~9 mg/L CRP

The sponsor included the following information in the labeling: "At 395 mg/dL triglycerides, there was a deviation of -11.2% per sample with a concentration of 4.15 mg/L CRP, and at 517 mg/dL triglycerides, there was a deviation of -10.5% per sample with a concentration of 0.83 mg/L CRP."

Prozone Effect

The sponsor provided data to support their claim that no prozone effect is observed up to CRP concentrations of 2044 mg/L.

4. Assay Reportable Range:

The assay has a reportable range of 0.2 mg/L to 10 mg/L.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Calibrator traceability to IRMM (Institute for Reference Materials and Measurements) ERM-DA472/IFCC is claimed, which is in turn traceable to the ERM-DA470/IFCC reference material.

6. Detection Limit:

The sponsor performed limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) studies following the recommendation in CLSI EP17-A2. The studies were conducted using 2 reagent lots, with each lot evaluated separately for each parameter.

For each reagent lot, the LoB was estimated using a non-parametric option described in the guideline using commercial depleted serum. The maximum LoB estimate was 0.09 mg/L.

The LoD was estimated following the non-parametric option described in the guideline using low-analyte serum samples. The maximum LoD estimate was 0.13 mg/L.

LoQ studies were performed by analyzing five low-concentration serum samples. The sponsor set a performance goal of <15% CV, and at 0.16 mg/L, the maximum imprecision observed was 13% CV.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The sponsor performed a method comparison study comparing results from the candidate method on the Yumizen C1200 to another legally marketed CRP assay.

One hundred and thirty-eight (138) serum samples, consisting of 124 patient samples and 14 spiked samples, spanning the measuring interval (0.2 mg/L to 10 mg/L), were tested in duplicate on the candidate method and a comparator method. The study was performed on 5 testing days.

A Passing-Bablok regression analysis using the first replicate for each method was performed, resulting in a slope of 0.9987, an intercept of -0.06852. The correlation coefficient (r-value) was reported as 0.995.

2. Matrix Comparison:

The sponsor conducted a study to evaluate the performance of lithium heparin plasma samples compared to serum samples. A total of 56 matched, native samples spanning the measuring range were evaluated on the candidate device.

The data were collected using 1 instrument and 1 lot of reagent. A Passing-Bablok regression analysis was performed using the first replicate of each matrix resulting in a slope of 0.9787, an intercept of 0.003012. The correlation coefficient (r-value) was reported as 0.998.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The sponsor provides the following information in the Expected Values section of the labeling based on literature*:

Typical clinical cutoff concentrations ≤ 1.0 mg/L

* Raifai N, Ridker PM. Population Distributions of C- reactive Protein in Apparently Healthy Men and Women in the United States: Implication for Clinical Interpretation. Clin Chem (2003) 49: 666-669.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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