510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k160712

B. Purpose for Submission:

Modification of the traceability of the assay from ERM-DA470 to ERM-DA474 and change in the Intended Use to remove the claim that the device can be used to evaluate the risk of developing coronary heart disease

C. Measurand:

C-reactive protein

D. Type of Test:

Immunoturbidimetric assay

E. Applicant:

Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products hsCRP Reagent

G. Regulatory Information:

Regulation section	Classification	Product code	Panel
21 CFR 866.5270	II	DCK	Immunology (82)

H. Intended Use:

1. Intended use(s):

   See Indication(s) for use

2. Indication(s) for use:
   VITROS Chemistry Products hsCRP Reagent is used on the VITROS 5,1 FS Chemistry System, the VITROS 4600 Chemistry System and the VITROS 5600 Integrated System

to quantitatively measure C-reactive protein (CRP) in human serum and plasma. CRP is used to evaluate conditions thought to be associated with inflammation in otherwise healthy individuals.

3. Special conditions for use statement(s):

   For prescription use only.
   For *in vitro* diagnostic use only.

4. Special instrument requirements:

   VITROS 5,1 FS Chemistry System
   VITROS 4600 Chemistry System
   VITROS 5600 Integrated System

I. Device Description:

The VITROS Chemistry Products hsCRP Reagent is being modified due to a change in the traceability of the assay. When initially cleared in k041799, the assay was traceable to ERM-DA470/IFCC and now the assay is traceable to ERM-DA474/IFCC. The reagent is otherwise unchanged since it was cleared in k041799.

The VITROS Chemistry Products hsCRP Reagent consists of two liquid reagents. Reagent 1 is a buffering solution that contains bovine serum albumin, a polymer, and a preservative. Reagent 2 contains latex particles coated with anti-CRP mouse monoclonal antibodies in a buffered solution and a preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Diazyme high sensitivity C-reactive protein (hsCRP) assay

2. Predicate 510(k) number(s):

   k103557

3. Comparison with predicate:

Similarities		
Item	Candidate Device VITROS Chemistry Products hsCRP Reagent	Predicate Diazyme hsCRP assay (k103557)
Intended Use	To quantitatively measure C-reactive protein (CRP) in human serum and plasma	Same

Similarities		
Item	Candidate Device VITROS Chemistry Products hsCRP Reagent	Predicate Diazyme hsCRP assay (k103557)
Principle	Immunoturbidimetric assay	Same
Sample type	Serum, plasma	Same

Differences		
Item	Candidate Device VITROS Chemistry Products hsCRP Reagent	Predicate Diazyme hsCRP assay (k103557)
Assay range	0.34–15.00 mg/L	0.20–20.00 mg/L
Assay traceability	IRMM Reference Material ERM-DA474/IFCC	IRMM Reference Material ERM-DA472/IFCC

K. Standard/Guidance Document Referenced (if applicable):

Clinical and Laboratory Standards Institute (CLSI) EP9-A3 "Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Third Edition"

CLSI EP6-A "Evaluation of the Linearity of Quantitative Measurement Procedures; Approved Guideline- First Edition"

CLSI EP17-A2 "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved-Second Edition"

L. Test Principle:

Samples are mixed with a buffering solution (Reagent 1), followed by the addition of anti-CRP antibodies coupled to latex microparticles (Reagent 2), which produces an immunochemical reaction yielding CRP antigen/antibody complexes. The turbidity is measured spectrophotometrically at 660 nm. Once a calibration has been performed for each reagent lot, the CRP concentration in each unknown sample can be determined using the stored calibration curve and the measured absorbance obtained in the assay of the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

To verify that precision has not changed as a result of the modification, three human serum sample pools with mean CRP concentrations of approximately 1, 10 and 14 mg/L were tested. Five replicates of three serum sample pools were run once per day for five days using two hsCRP Reagent lots and two Calibrator Kit 17 lots across three VITROS Chemistry Systems. The total imprecision estimates include within run and between run. The sponsor concluded that the precision claims are unchanged. The results are summarized below:

Analyzer	Reagent Lot	Mean Conc. (mg/L)	Within run		Between run		Total	
			SD	%CV	SD	%CV	SD	%CV
VITROS 5,1 FS	1	0.96	0.067	6.96	0.000	0.00	0.067	6.96
		9.65	0.104	1.08	0.080	0.83	0.132	1.37
		13.41	0.156	1.16	0.081	0.60	0.176	1.31
	2	1.02	0.060	5.90	0.024	2.36	0.065	6.39
		9.89	0.151	1.53	0.124	1.25	0.196	1.98
		13.86	0.266	1.92	0.134	0.97	0.298	2.15
VITROS 4600	1	0.97	0.063	6.53	0.000	0.00	0.063	6.53
		9.52	0.188	1.97	0.000	0.00	0.188	1.97
		13.12	0.269	2.05	0.067	0.51	0.277	2.11
	2	1.01	0.047	4.66	0.021	2.08	0.052	5.16
		9.79	0.253	2.58	0.144	1.47	0.291	2.97
		13.64	0.400	2.93	0.078	0.57	0.408	2.99
VITROS 5600	1	0.92	0.053	5.77	0.000	0.00	0.053	5.77
		9.34	0.081	0.87	0.081	0.87	0.115	1.23
		12.78	0.126	0.99	0.110	0.86	0.167	1.31
	2	1.00	0.054	5.40	0.000	0.00	0.054	5.4
		9.54	0.113	1.18	0.121	1.27	0.165	1.73
		13.26	0.278	2.10	0.148	1.12	0.315	2.38

b. Linearity/assay reportable range:

The linearity study followed the recommendations in CLSI EP6-A. A high CRP concentration serum pool was mixed with different proportions of a low CRP serum sample to generate 13 concentrations ranging from 0.040 to 17.5 mg/L. Each sample was tested in triplicate determinations on the VITROS 5,1 FS Chemistry System, VITROS 4600 Chemistry System and the VITROS 5600 Integrated System. Linear results were compared to 2nd and 3rd order polynomial fits against a pre-specified allowable error. The deviation of linearity was found to be no more than 13.7% within the claimed linear interval.

The sponsor claims a linearity range of 0.34 to 15.0 mg/L.

The following table summarizes the results obtained for the linear regression generated on each instrument:

Instrument	Slope	y-intercept	R^2
VITROS 5,1 FS Chemistry System	0.9817	0.1126	0.9991
VITROS 4600 Chemistry System	0.9483	0.0221	0.9975
VITROS 5600 Integrated System	0.9428	-0.0053	0.9964

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability:

The assay is now traceable to the IRMM (Institute for Reference Materials and Measurements) ERM-DA474/IFCC Reference Material, which in turn is traceable to the ERM-DA470 reference material.

d. *Detection limit:*

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined according to CLSI EP17-A2. The LoB and LoD estimates were evaluated separately for each reagent lot on each VITROS Chemistry System and the reagent lot and analyzer combination yielding the highest value was used for the LoB, LoD and LoQ claims.

To determine the limit of the blank (LoB), five replicates of three blank samples were run once per day for three days using two hsCRP Reagent lots and two Calibrator Kit 17 lots on three VITROS Chemistry Systems (i.e., 1 VITROS 5,1 FS Chemistry analyzer, 1 VITROS 4600 Chemistry analyzer and 1 VITROS 5600 Integrated analyzer) for a total of 90 measurements per reagent lot per system (and 540 total test results). The LoB data were assessed nonparametrically. The blank sample measurements were sorted from lowest to highest for each reagent lot and analyzer. The LoB was determined to be 0.21 mg/L.

To determine the limit of the detection (LoD) and Limit of Quantitation (LoQ), human serum samples with concentrations ranging from approximately 0.2 mg/L to 0.5 mg/L CRP were prepared. Five replicates of four patient samples were run once per day for five days using two hsCRP Reagent lots and two Calibrator Kit 17 lots across three VITROS Chemistry Systems totaling 1200 determinations (50 measurements per lot per sample for each system). The Limit of Detection (LoD) was calculated parametrically following the recommendations in the CLSI guideline. The LoD was determined to be 0.26 mg/L.

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 0.34 mg/L based on the sample/instrument/reagent lot combination with the highest imprecision observed in the study (<13%CV).

The measuring range is 0.34 mg/L to 15 mg/L.

e. Analytical specificity:

The reagent is identical to the reagent cleared in k041799. The analytical specificity study was conducted in k041799 and the claims are unchanged.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

One hundred and nineteen unmodified serum samples were tested using the candidate device on the VITROS 5600, 4600, and 5,1 Systems and the predicate method. Of the 119 samples tested 113 were within the measuring range of both the VITROS hsCRP assay and the predicate device. The samples had concentrations ranging from 0.37 to 17.97 mg/L.

An ordinary least squares linear regression analysis of the VITROS hsCRP assay on the VITROS 5600 System versus the predicate device was performed. The results are summarized below:

$$Y = 1.02\ X + 0.26, \text{ correlation coefficient} = 0.99$$

The results from the VITROS Chemistry Products hsCRP Reagent on the VITROS 4600 and VITROS 5,1 Chemistry Systems were also used to compare with the results using the VITROS 5600 Integrated System using ordinary least squares linear regression analysis. The samples had concentrations ranging from ≈ 0.4 to ≈15 mg/L. The results are summarized below:

System	N	Slope (95% CI)	y-intercept (95% CI)	Correlation coefficient
VITROS 4600 vs. VITROS 5600 System	110	1.02	0.01	1.00
VITROS 5,1 FS vs. VITROS 5600 System	109	1.07	0.11	1.00

b. Matrix comparison:

The reagent is identical to the reagent cleared in k041799. Comparison studies between serum and lithium heparin plasma samples were conducted in k041799 and the claims are unchanged.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:
The sponsor verified the reference interval established using the predicate device following the recommendations in the CLSI guideline EP28-A3c "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition" by using serum samples from 47 apparently healthy subjects. The sponsor claims a reference interval of <5 mg/L.

The sponsor also provides the following information in the package insert:
Reference intervals may differ for each population studied and therefore each laboratory should confirm the validity of these intervals for the population it serves. Increases in CRP values are non-specific and should be interpreted together with a complete clinical history. Follow-up testing of patients with elevated CRP values should be performed.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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