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

A. 510(k) Number:

k173833

B. Purpose for Submission:

New device

C. Measurand:

C-reactive protein (CRP)

D. Type of Test:

Quantitative, immunoturbidimetric assay

E. Applicant:

SENTINEL CH. S.p.A.

F. Proprietary and Established Names:

CRP Vario

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.5270

2. Classification:

   Class II

3. Product code:

   NQD (Cardiac C-Reactive Protein, Antigen, Antiserum, And Control)

4. Panel:

   82 – Immunology

H. Intended Use:

1. Intended use(s):

   Refer to Indications for Use below.

2. Indication(s) for use:

   The CRP Vario assay is intended for the quantitative immunoturbidimetric determination of C-reactive protein in human serum or plasma. Cardiac CRP High Sensitive (cCRP) may be used for aid in identification and stratification of individuals at risk for cardiovascular disease. When used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, the cCRP may be useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndrome.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Performance data for this submission was collected on the Abbott Architect c8000 analyzer.

I. Device Description:

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

Reagents

Component	Reactive ingredients	Inactive ingredients
Reagent 1	Glycine buffer	Bovine albumin, sodium azide
Reagent 2	Anti-CRP polyclonal antibodies (rabbit) adsorbed on latex particles	Bovine albumin, sodium azide

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dade Behring CardioPhase hsCRP

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

   k033908

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Same	For the quantitative determination of C-reactive protein (CRP) in human serum and plasma
Recommended anticoagulants	Same	Heparin, EDTA

Differences		
Item	Device	Predicate
Measuring Range	0.3 – 10.0 mg/L	0.175 – 20.0 mg/L
Calibrator Levels	3	6
Limit Of Quantitation	0.3 mg/L	0.175 mg/L
Standardization	ERM-DA472/IFCC standard	IRMM Reference Material CRM 470
Assay Principle	Turbidimetric / Immunoturbidimetric	Particle enhanced immunonephelometry
Antibody	Rabbit Polyclonal	Mouse Monoclonal

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

- Points to Consider for Collection of Data in Support of In-Vitro Device Submissions for 510(k) Clearance issued on December 26, 1994.
- Format for Traditional and Abbreviated 510(k)s - Guidance for Industry and FDA Staff issued on August 12, 2005.
- Review Criteria for Assessment of C-Reactive Protein (CRP), High C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays. Issued on September 22, 2005.
- Clinical and Laboratory Standards Institute (CLSI) EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition, 2012
- CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition, 2005

- CLSI EP6-A: Evaluation of the Linearity of Quantitive Measurement Procedures: AStatistical Approach; Approved Guideline, 2003
- EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition, 2014
- CLSI EP21: Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline, 2003

L. Test Principle:

CRP Vario is a latex immunoassay designed to quantitatively measure blood CRP levels in serum and plasma. When an antigen-antibody reaction occurs between CRP in a sample and anti CRP antibody, which has been adsorbed to latex particles, agglutination results. This agglutination is detected as an absorbance change, with the rate of change being proportional to the quantity of CRP in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The precision performance of the device was evaluated over 20 days by assaying eight CRP concentrations (levels). Levels 1 – 4 were native patient serum samples targeted near the medical decision point of 1 mg/L and were diluted using either synthetic serum or low native patient serum samples. Level 5 was a control material and levels 6 - 8 were serum samples spiked with CRP. The target concentrations for each level are listed below:

Sample	Sample Matrix	CRP Vario Concentration (mg/L)
Level 1	Serum	0.40
Level 2	Serum	0.60
Level 3	Serum	1.0
Level 4	Serum	2.0
Level 5	CRP High Sensitivity Control	0.5
Level 6	Serum	4.00
Level 7	Serum	6.00
Level 8	Serum	8.00

The samples were tested in 2 replicates, 2 times per day, for a total of 20 testing days, using one analyzer and one lot of reagents.

The mean concentration value, within-run SD and percent coefficient of variation (%CV), between-run SD and %CV, and between-day SD and %CV were calculated for each sample. The within-laboratory (total) SD and %CV were estimated using

the summation of the within-run, between-run, and between-day variance components, as summarized in the tables below:

Sample	N	Mean (mg/L)	Within-Run		Between-Run	
			SD	%CV	SD	%CV
Level 1	80	0.34	0.011	3.2	0.021	6.3
Level 2	80	0.53	0.007	1.4	0.033	6.3
Level 3	80	0.98	0.012	1.3	0.020	2.1
Level 4	80	1.81	0.013	0.7	0.040	2.2
Level 5	80	0.52	0.010	1.9	0.004	0.7
Level 6	80	4.32	0.030	0.7	0.033	0.8
Level 7	80	6.07	0.047	0.8	0.061	1.0
Level 8	80	8.24	0.043	0.5	0.056	0.7

Sample	N	Mean (mg/dL)	Between-Day		Within- Laboratory	
			SD	%CV	SD	%CV
Level 1	80	0.34	0.023	6.9	0.033	9.9
Level 2	80	0.53	0.023	4.4	0.041	7.7
Level 3	80	0.98	0.010	1.0	0.026	2.6
Level 4	80	1.81	0.031	1.7	0.052	2.9
Level 5	80	0.52	0.000	0.0	0.011	2.0
Level 6	80	4.32	0.033	0.8	0.055	1.3
Level 7	80	6.07	0.000	0.0	0.077	1.3
Level 8	80	8.24	0.012	0.1	0.072	0.9

b. Linearity/assay reportable range:

A linearity study was performed following the recommendations in CLSI EP06-A. A high serum pool with a CRP concentration of 11.88 mg/L (measured with a different CRP method which allows measurement above 10.00 mg/L) was prepared by spiking patient serum pool with CRP. A low serum pool with a CRP concentration of 0.10 mg/L was prepared by diluting patient serum with saline. The low and high serum pools were then combined in varying proportions to create ten samples (Levels 1 – 10) covering the analytical measuring interval (AMI) of 0.30 mg/L to 10.00 mg/L. Each sample was tested in replicates of 8 and the difference in recovery between the expected concentration and the measured concentration at each level did not exceed more than 4%.

Linear regression analysis produced a slope of 1.006, an intercept of -0.020 and an r value of 0.9998.

The sponsor concluded that the results of the linearity study supported the claimed measuring interval of 0.3 to 10.0 mg/L.

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

Assay traceability to CRM 472 (which is traceable to CRM470) is claimed.

d. *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 two 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 samples with no analyte. The maximum LoB estimate was 0.02 mg/L.

The LoD was estimated following the parametric option described in the guideline using low-analyte serum samples. The maximum LoD estimate was 0.04 mg/L.

LoQ studies were performed by analyzing eight low concentration serum samples. The precision profile approach described in the guideline was used to estimate the LoQ. The LoQ was defined as the lowest concentration that can meet a 20% CV and the maxium LoQ estimate was 0.07 mg/L. The claimed LoQ in the package insert is 0.30 mg/L.

e. *Analytical specificity:*

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.

The control and test samples were tested in a minimum of eight replicates, using one instrument and one lot of each reagents.

Potential interferents were evaluated at the concentrations listed below. For each analyte, the difference (mg/dL) and the percent difference were calculated between each test sample and the corresponding control sample using the following equations:

Difference = Test sample mean concentration - Control sample mean concentration

% difference = (difference/control sample mean concentration) x 100

At the concentrations tested, the maxium observed % difference was $\leq \pm$ 10 %. The data provided supports the sponsor's claims that no interference was seen at the concentrations tested below:

- Hemoglobin - up to 1984 mg/dL
- Unconjugated Bilirubin up to 51.0 mg/dL
- Conjugated Bilirubin - up to 62.0 mg/dL
- Lipemia (as Intralipid) - up to 500 mg/dL
- Human Triglyceride up to 2949 mg/dL
- Total Protein (Gamma Globulin) - up to 12.0 g/dL
- Rheumatoid Factor - up to 243.95 IU/mL

High Dose Hook Effect

The sponsor provided data to support their claim that no hook effect is observed up to CRP concentrations of 1500 mg/L.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method Comparison

The sponsor performed a method comparison study comparing results from the candidate method on the ARCHITECTc8000 System to the predicate assay.

One lot of CRP Vario reagents were evaluated in this study.

One hundred and fifteen (115) serum patient samples with concentrations spanning the measuring interval (0.3 - 10.0 mg/L) were tested in singlicate on the candidate method and predicate method. The study was performed on three testing days.

A Passing-Bablok linear regression was performed, resulting in a slope of 1.019, an intercept of 0.061 and a correlation coefficient (r-value) of 0.996.

b. Matrix comparison:

The sponsor conducted a study to evaluate the performance of different sample

collection tubes for serum and plasma when compared with serum from a plastic tube without gel. For each tube type, a total of 40 native samples spanning the measuring range were evaluated.

The data was collected using 1 instrument, and 1 lot of reagent. A Passing-Bablok linear regression analysis was performed using the first replicate of the test matrix (i.e., the different sample collection tubes for serum and plasma) and the mean of the first 2 replicates of the comparator matrix (i.e., serum from a plastic tube without gel).

Linear regression analysis produced the following:

Tube types	slope	intercept	r
serum non-gel (x) vs. serum gel	1.01	-0.01	0.9977
serum non-gel (x) vs. EDTA non-gel	0.99	0.000	0.9940
serum non-gel (x) vs. Li Hep gel	0.96	0.02	0.9916
serum non-gel (x) vs. Na Hep non-gel	0.97	0.01	0.9924

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 provides the following information in the Expected Values section of the labeling*

Relative Risk	Range (mg/dL)
Low	< 0.1
Average	1.0 – 3.0
High	> 3.0

* Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107(3):499–511.

*Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363-369.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

O. Conclusion:

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