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

A. 510(k) Number:
K040241

B. Purpose for Submission:
Clearance of CRP assay

C. Analyte:
C-Reactive Protein (CRP)

D. Type of Test:
Turbidometric immunoassay

E. Applicant:
Genzyme, Inc.

F. Proprietary and Established Names:
N-Geneous Wide Range CRP Reagent
N-Geneous Wide Range CRP Calibrator

G. Regulatory Information:
1. Regulation section:
   21 CFR § 866.5270, C-reactive protein immunological test system
   862.1150, Calibrator
2. Classification:
   Class II
3. Product Code:
   DCK, C-reactive protein, antigen, antiserum, and control
   JIS, Calibrator, primary
4. Panel:
   Immunology (82)

H. Intended Use:
1. Intended use(s):

   The N-Geneous Wide Range CRP Reagent is intended for the quantitative measurement of C-Reactive Protein (CRP) concentration in serum or plasma.

   Measurement of CRP is useful for determining the existence of inflammatory lesions and to monitor treatment.

The N-Geneous Wide Range CRP Calibrator is intended for the calibration of the N-Geneous Wide Range CRP assay.

2. <u>Indication(s) for use:</u>
   See Intended Use section.

3. <u>Special condition for use statement(s):</u>
   For in vitro diagnostic use.

   Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

4. <u>Special instrument Requirements:</u>
   Clinical chemistry analyzers (testing performed on Roche Hitachi 912 analyzer)

I. Device Description:

The N-Geneous Wide Range CRP assay consists of two wet reagents. Reagent 1 is a buffering solution and Reagent 2 contains latex beads coated with mouse monoclonal anti-human CRP antibodies. The assay is for use on general clinical chemistry analyzers.

J. Substantial Equivalence Information:

1. <u>Predicate device name(s):</u>
   Dade Behring N High sensitivity CRP assay
   Dada Behring N Rheumatology Standard SL
2. <u>Predicate K number(s):</u>
   K991385
   K964527
3. <u>Comparison with predicate:</u>

Similarities		
Item	**Device**	**Predicate**
Intended Use	Quantitative measurement of CRP in serum or plasma	Quantitative measurement of CRP in serum or plasma
Sample Matrix	Serum or plasma	Serum or plasma
Antibody	Mouse monoclonal anti-human CRP	Mouse monoclonal anti-human CRP
Differences		
Item	**Device**	**Predicate**
Assay Range	0.12 to 320 mg/L	0.175 to 11 mg/L
Antibody substrate	Latex beads	Polystyrene beads
Number of calibrators	5	1

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

NCCLS Guideline EP9-A - Method Comparison and Bias Estimation Using Patient
          Samples
NCCLS Guideline EP5-A - Evaluation of Precision Performance of Clinical Chemistry
          Devices
NCCLS Guideline EP6-A - Evaluation of the Linearity of Quantitative Analytical
          Methods
NCCLS Guideline EP7-A - Interference Testing in Clinical Chemistry
NCCLS Guideline C28-A - How to Define and Determine Reference Intervals in the
          Clinical Laboratory

L. Test Principle:

Sample is mixed with the buffer solution and the anti-CRP antibody–coated beads. CRP
in the sample binds the antibody-coated beads and agglutinates. The light scattering
caused by an increase in particle size is measured. The amount of light scattering is
proportional to the concentration of CRP in the sample.

M. Performance Characteristics (if/when applicable):
      1. <u>Analytical performance:</u>
          a. Precision/Reproducibility:

Device imprecision was evaluated according to NCCLS EP5-A. Spiked serum samples
were run in duplicate twice per day for 20 days (units = mg/L).

Control	Mean	Within Run		Total	
		SD	% CV	SD	% CV
1	0.30	0.02	5.5	0.02	6.7
2	1.00	0.02	1.8	0.02	2.3
3	2.97	0.04	1.3	0.05	1.7
4	51.3	0.61	1.2	0.96	1.9
5	202	3.0	1.5	3.1	1.5

          b. Linearity/assay reportable range:

The useable range of this device is 0.12 – 320 mg/L (the Limit of Quantification to the
upper end of the linear range).

Linearity was assessed using two separate sets of samples to cover the range (range
covered = 0.6 – 337 mg/L). Two sets of CRP-stripped serum samples were spiked with
human CRP to values of 55 or 360 mg/L. The two spiked samples were then mixed with
the same (unspiked) CRP-stripped serum matrix to result in a set of samples with
predicted CRP concentrations that covered the assay range. The samples were assayed
and the results were compared to the concentrations calculated from the dilution factors
of the original samples. Results are summarized below (units = mg/L).

Set	Expected	Observed	Bias to Expected	Bias to Observed
A	0.00	0.01	0.01	----
A	56.19	53.98	-2.21	-4 %
A	112.38	110.49	-1.89	-2 %
A	224.75*	224.75	-----	-----
A	337.13	337.27	0.14	0 %
B	0.00	0.02	0.02	-----
B	0.55	0.63	0.08	14 %
B	1.11	1.24	0.13	12 %
B	5.54	5.50	-0.04	-1 %
B	11.07	10.33	-0.74	-7 %
B	22.14	20.41	-1.73	-8 %
B	27.68	26.34	-1.33	-5 %
B	33.21	32.72	-0.49	-1 %
B	44.28	44.51	0.23	1 %
B	55.35*	55.35	-----	-----

*Sponsor assumed 100% recovery for these samples

The results above indicate that the assay is linear across the measuring range of the assay.

To test the dilution recovery of high samples, 5 patient samples with CRP values ranging from 200 to 360 mg/L were diluted up to 5X with saline and measured in quadruplicate. The sponsor states that expected results were recovered for all samples (expected is defined as within +/- 10%).

> c. *Traceability (controls, calibrators, or method):*

The device is calibrated by a set of 5 calibrators (sold separately) with targeted CRP concentrations of 3, 6, 30, 170, and 360 mg/L. The calibrator is traceable to CRM470. A master calibrator is prepared and value assigned by multiple measurements of multiple lots using the device. The calibrators are traceable to this master calibrator and are value assigned using the device. Stability testing is described.

> d. *Detection limit:*

Functional sensitivity, defined as the lowest concentration at which the assay performs with 20% CV, was assessed by measuring 4 serum samples 15 times in each of 3 runs (for n = 45 for each sample). By this method, the functional sensitivity of this assay is said to be 0.12 mg/L (derived by extrapolation of plot of concentration vs. % CV). Results are summarized below (units = mg/L).

Mean CRP Concentration	SD	% CV
0.32	0.024	7.7 %
0.15	0.022	14.5 %
0.10	0.025	24.9 %
0.08	0.021	25.7 %

The analytical sensitivity was defined as the lowest concentration distinguishable from zero. Saline was run 20 times on the assay and the mean plus two standard deviations was calculated as 0.04 mg/L.

e. Analytical specificity:

Interference of endogenous substances was evaluated by testing for the effect of hemoglobin (up to 1000 mg/dL), ascorbic acid (up to 500 mg/dL), bilirubin (up to 60 mg/dL), Intralipid (up to 3%), Rheumatoid factor (153 – 1711 IU/mL), and HAMA (100 – 194 ng/mL) on serum samples containing a nominal concentration of 3 mg/L. The only interference observed was a bias of >0.3 mg/L at Intralipid concentrations > 0.8 % (~2400 mg/dL triglyceride equivalent). Interference was defined as a result +/- 10 % of the control. This information is in the package insert.

To test exogenous interferences (defined as a result +/- 10 % of the control), 27 common drugs were tested for their effect on a serum sample with a nominal CRP concentration of 3 mg/L. No interferences were seen. The list of tested drugs and their concentrations can be found in the package insert.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Serum samples (n=229) ranging from 0.2 to 198 mg/L were measured using the device and comparing those measurement to those made with the predicate device. Samples that had CRP concentrations above the measuring range of the predicate device were diluted before measurement and then multiplied by the dilution factor per the predicate labeling. Results are summarized below.

All Samples: Device = 1.05(Predicate) – 0.31; r = 0.995
                Standard Error: 0.012 (slope) and 0.263 (intercept)
                95% CI: 1.03 – 1.07 (slope) and -0.83 – 0.21 (intercept)

Samples <0.5: Device = 1.02(Predicate) + 0.08
                95% CI: 0.86 – 1.17 (slope) and 0.03 – 0.13 (intercept)

Samples <10.0: Device = 0.94(Predicate) + 0.1; r = 0.995

Samples >50: Device = 1.10(Predicate) – 12.9
   95% CI: 0.92 – 1.29 (slope) and -40.9 – 15.2 (intercept)

   b. *Matrix comparison:*

Samples from 18 patients were collected as matched serum, Na heparin plasma, Li heparin plasma, and EDTA plasma samples. Samples were measured in quadruplicate and results were compared. There were no significant differences observed between sample types.

Sample stability was assessed and no significant bias was observed when samples were held at 25°C, 2-8°C, or -20°C for 5, 13, or 36 days. No significant bias was observed when samples were subjected to two freeze-thaw cycles for either serum or plasma.

   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 references a study of 22,403 apparently healthy individuals and cites CRP ranges (5th -95th percentiles) of 0.19 – 9.14 mg/L for women and 0.28 – 8.55 mg/L for men.

The sponsor states that they performed a small study of 50 apparently healthy men and women (25 of each). They state that their results are in line with their referenced study.

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