

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

A. 510(k) Number:

k080662

B. Purpose for Submission:

New device

C. Measurand:

Cystatin C

D. Type of Test:

Quantitative, particle enhanced turbidimetric immunoassay

E. Applicant:

Genzyme Corporation

F. Proprietary and Established Names:

Genzyme Cystatin C Reagent
Genzyme Cystatin C Calibrator

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NDY	Class II	862.1225	75, Chemistry
JIT	Class II	862.1150	75, Chemistry

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The Genzyme Cystatin C is an in vitro diagnostic test intended for the quantitative

measurement of Cystatin C concentration in human serum, heparinized plasma and EDTA plasma. Cystatin C measurements are used as an aid to the diagnosis and treatment of renal diseases.

Calibrator: For the calibration of Genzyme Cystatin assay. For In Vitro Diagnostic Use.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Clinical chemistry analyzers (testing was performed on the Abbott Aeroset Automated Analyzer).

I. Device Description:

The Genzyme Cystatin C assay kit consists of the following:

1. Cystatin C Reagent 1, Buffer Solution: a buffer solution adjusted to pH 6.7. It is preserved with sodium azide and is ready to use.
2. Cystatin C Reagent 2, Colloidal Gold Particles: colloidal gold, coated with rabbit polyclonal antibodies. It is preserved with sodium azide and is ready to use.
3. Cystatin C Calibrators: calibrators consist of a bovine serum albumin liquid matrix with assigned concentrations of cystatin C. The calibrators, labeled 1 through 6, have approximate values of 0.0, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/L respectively. Each is preserved with sodium azide and is ready to use.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Dade Behring N Latex Cystatin C

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

k041878

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Analyte	Cystatin C	Cystatin C
Intended Use	For the quantitative measurement of cystatin C concentration in human serum, heparinized plasma and EDTA plasma. Cystatin C measurements are used as an aid to the diagnosis and treatment of renal diseases.	For the quantitative determination of cystatin C in human serum and heparinized plasma. Cystatin C measurements are used in the diagnosis and treatment of renal diseases.
Antibody	Rabbit	Rabbit
Format	Liquid	Liquid
Use of Calibrators	Yes	Yes

Differences		
Item	Device	Predicate
Sample Matrix	Serum or LiHeparin Plasma, or EDTA Plasma	Serum or Heparinized Plasma
Reference Interval	0.61 – 1.17 mg/L	0.53 – 0.95 mg/L
Technology / Methodology	Particle enhanced immunoturbidimetric assay using colloidal gold agglutination	Particle enhanced immunonephelometry using polystyrene particles agglutination
Number of Calibrators	6	1

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

- CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition (2004)
- CLSI EP6-A: Evaluation of Linearity of Quantitative Measurement Procedures, A Statistical Approach: Approved Guideline (2003)
- CLSI EP7-A: Interference Testing in Clinical Chemistry; Approved Guideline (2002)
- CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004)
- CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (2002)
- CLSI C28-A2, How to define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline

L. Test Principle:

Genzyme Cystatin C is based on the sol particle turbidimetric immunoassay principle. It contains colloidal gold particles coated with anti-cystatin C specific polyclonal antibodies. The reaction between the particles and any cystatin C in samples results in the formation of agglutinates and an associated change in absorbance signal. The change in absorbance signal is proportional to the amount of cystatin C in the sample. Cystatin C concentration in the sample is determined by comparison with a standard curve.

M. Performance Characteristics (if/when applicable):

All performance testing was performed on the Abbott Aeroset Automated Analyzer.

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility studies were conducted by testing four levels controls and three serum pools. The samples were run in duplicate, twice a day for twenty days using one lot and one instrument. The results are presented in the table below:

Control	Mean	Within-Run		Total	
	mg/L	SD	CV%	SD	CV%
Control A1	0.52	0.01	2.8	0.02	3.6
Control A2	2.10	0.02	0.7	0.03	1.3
Control B1	0.33	0.02	5.0	0.02	6.4
Control B3	0.67	0.01	1.6	0.01	1.8
Serum					
Low Serum Pool	0.72	0.01	1.7	0.02	2.3
Med Serum Pool	2.79	0.02	0.7	0.04	1.3
High Serum Pool	5.06	0.08	1.5	0.12	2.4

b. *Linearity/assay reportable range:*

Linearity across the assay range was confirmed by inter diluting a sample spiked (high sample) with cystatin C with a cystatin C free serum sample across the range of 0 to 10mg/L to create nine additional samples. Each sample was tested in replicates of ten. The linear regression equation was $y = 0.96x - 0.18$, $R^2 = 0.9917$. The reportable range of the assay is 0.2 – 8.0 mg/L (the value of the highest calibrator).

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

The Cystatin C calibrator is traceable to a stock of concentrated recombinant Cystatin C Standard. There is no internationally recognized reference standard for cystatin C. The calibrator has six levels (0-8.0 mg/L). The high calibrator is prepared directly from the source material, then serially diluted to achieve the remaining concentrations. All lots are run against the in-house primary standard calibration material for final value assignment.

Quality controls are recommended, but not supplied by the sponsor.

Accelerated and real time stability studies have been conducted. Protocols and acceptance criteria were described and found to be acceptable. The manufacturer claims the following:

Unopened stored at 2-8 °C the assay reagent and calibrator are good until the expiration date.

After opening stored at 2-8 °C the assay reagent and calibrator are good for 4 weeks.

d. *Detection limit:*

The Limit of Blank (LoB) - a blank sample was assayed on multiple instrument channels in replicates of five twice a day for five days for a total of 165 replicates. The LoB was determined to be 0.02 mg/L.

The Limit of Detection (LoD) – 12 low level samples with concentrations less than 4 mg/L and assayed in 10 replicates. The pooled SD for the samples was 0.02 mg/L. The LoD was determined to be 0.05 mg/L.

The Limit of Quantitation (LoQ) – The sponsor defined the LoQ as where the CV is less than or equal to 10% (with the low end samples' pooled standard deviation at 0.02 mg/L). The LoQ is 0.20 mg/L

e. *Analytical specificity:*

Two serum samples containing cystatin C at concentrations of 0.44 mg/L and 1.30 mg/L were evaluated for interference. Sponsor states that no significant interference is defined as cystatin C <1 mg/L observed value to be within \pm 0.1 mg/L and \geq 1 mg/L observed value to be within \pm 10% of the control sample. The following substances demonstrated no significant interference:

Substance Tested	Test Concentration	High cystatin C	Low cystatin C
Bilirubin (unconjugated)	20 mg/dL	97.2%	-0.08
Bilirubin (conjugated)	50 mg/dL	101.9%	0.02
Triglyceride	940 mg/dL	97.8%	-0.1
Hemoglobin	900 mg/dL	105%	0.06
Rheumatoid Factor	800 IU/mL	0.1	0.06

A list of other compounds were evaluated for interference and found to have no significant interference or cross reactivity. A list of these compounds is present in the product labeling.

Hook effect- The hook effect of the Genzyme cystatin C immunoassay was evaluated by using a spiked serum sample (25 mg/L) and making a serial dilution and tested. The sponsor claimed that there is no observed hook effect up to 25 mg/L.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A split sample method comparison study was conducted between the Genzyme Cystatin C method and the Dade-Behring N Latex Cystatin C method. 148 serum samples ranging from 0.48 to 7.73 mg/L were tested on the Abbott Aeroset analyzer and Dade Behring BNII analyzer. The correlation is $y = 1.11x + 0.10$ with a r^2 of 0.997.

The data demonstrate a slight positive bias compared to the predicate device, but the correlation was strong. This data, in conjunction with the sponsor's reference range study (see below) allow the device to be labeled so that users can adequately interpret results.

b. Matrix comparison:

A serum / plasma comparison test was performed for the Genzyme Cystatin C assay. 56 serum samples were compared to matched Lithium Heparin and EDTA plasma samples. Of the 56 samples 41 were native of which 9 were

from know renal deficient patients and 15 samples were spiked. The correlations are as follows:

Matrix	n	Slope	Intercept	r	Device range (mg/L)
Li Heparin vs. Serum	55	0.9767	0.0396	.996	0.68 – 4.72
EDTA vs. Serum	48	1.006	-0.0035	0.999	0.69 - 4.77

The sponsor states in the labeling that serum, Lithium heparin, and EDTA samples can be used for the Genzyme cystatin C determination.

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 conducted a normal range study using 196 normal samples from apparently healthy individuals (101 males and 95 females). The reference range interval was calculated using non-parametric statistics and represents the central 95% of the population. Package insert states that each laboratory should establish its own expected ranges.

Cystatin C – 0.61-1.17 mg/L

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.