

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

A. 510(k) Number:

k063351

B. Purpose for Submission:

New Device

C. Measurand:

Cystatin C

D. Type of Test:

Quantitative, particle-enhanced immunonephelometry

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Dimension Vista™ CYSC Flex® reagent cartridge
Dimension Vista™ Protein 3 Calibrator
Dimension Vista™ Cystatin C Control Low
Dimension Vista™ Cystatin C Control High

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NDY	II	§862.1225 Creatinine test system	Chemistry
JIX	II	§862.1150 Calibrator secondary	Chemistry
JJY	I	§862.1660 Single (specified) analyte controls (assayed and unassayed)	Chemistry

H. Intended Use:

1. Intended use(s):

See Indications for use below.

2. Indication(s) for use:

Dimension Vista™ CYSC Flex® reagent cartridge:

The CYSC method is an in vitro diagnostic test for the quantitative determination of cystatin C in human serum, heparinized plasma or EDTA plasma on the Dimension Vista® System. Cystatin C measurements are used in the diagnosis and treatment of renal diseases.

Dimension Vista™ Protein 3 Calibrator:

The PROT3 CAL is an in vitro diagnostic product to the calibration of the Cystatin C (CYSC) and Microalbumin (MALB) methods on the Dimension Vista® System.

Dimension Vista™ Cystatin C Control L and H:

CYSC CON L and H are assayed intralaboratory quality controls for the assessment of precision and analytical bias in determination of cystatin C (CYSC) on the Dimension Vista® System.

For *in vitro* diagnostic use.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Dade Behring Dimension Vista® System

I. Device Description:

The Cystatin C Reagents, Calibrators and Controls are designed to be used on the Dade Behring Dimension Vista® System.

Reagents:

Wells ^{a, b}	Form	Ingredient	Concentration ^c	Source
1-2	Liquid	CYSC Supplement Reagent 1: Phosphate Buffer, Immunoglobulin	0.5 g/L	Rabbit
3-4	Liquid	CYSC Supplement Reagent 2: Polyethylene Glycol Sorbitan Monolaurate	85.0 g/L	
11- 12	Liquid	CYSC Reagent ^d : Polystyrene Particles, Antibodies to human Cystatin C	2.25 g/L 30.0 mg/L	Rabbit

- a) Wells are numbered consecutively from the wide end of the cartridge
- b) Contains preservatives
- c) Nominal value per well in a cartridge
- d) Antibody titer may vary from lot to lot.

Calibrators:

Dimension Vista™ Protein 3 Calibrator

PROT3 Cal is a multi-analyte, lyophilized, polygeline based product containing urinary cystatin C and serum albumin of human origin.

Contents: 4 vials, (4A, each for 1.0 mL)

Assigned Constituent Values:

Constituent	Traceability
CYSC	Highly purified proteins
MALB	Protein reference preparation ERM®-DA470 (CRM 470) ^{1,2}

Controls:

CYSC CON L and H are assayed intra-laboratory quality controls for the assessment of precision and analytical bias in determination of cystatin C (CYSC) on the Dimension Vista® System. Both CYSC CON L and H is a lyophilized polygeline based product with urinary proteins of human origin containing cystatin C. Each CYSC CON L and H control kit contains (4 - 1.0 mL) vials of CYSC CON L or H control material. The expected maximum observed standard deviation for repeatability (within-run precision) using n = 5 replicates at the following nominal cystatin C concentrations are:

Standard Deviation mg/L (%CV)

Material	Mean mg/mL	Repeatability	Within-Lab
CYSC CON L	1.04	0.03 (2.87)	0.04 (3.69)
CYSC CON H	2.05	0.05 (2.25)	0.07 (3.35)

Controls levels are automatically prepared and corresponding values calculated by the instrument.

J. Substantial Equivalence Information:

**Comparative Features
N Latex Cystatin C Kit vs. Dimension Vista™ CYSC Assay**

Feature	N Latex Cystatin C Kit (k041878)	Dimension Vista™ CYSC Assay (k063351)
Intended Use	N Latex Cystatin C is an in vitro diagnostic kit containing reagents for the quantitative determination of cystatin C in human serum and heparinized plasma by means of particle-enhanced immunonephelometry using BN™ Systems. Cystatin C measurements are used in the diagnosis and treatment of renal diseases.	The CYSC method is an in vitro diagnostic test for the quantitative determination of cystatin C in human serum, heparinized plasma or EDTA plasma on the Dimension Vista® System. Cystatin C measurements are used in the diagnosis and treatment of renal diseases.
Principle	Polystyrene particles coated with specific antibodies to human cystatin C are aggregated when mixed with samples containing human cystatin C. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by comparison with a standard of known concentration.	Polystyrene particles coated with specific antibodies to human cystatin C are aggregated when mixed with samples containing human cystatin C. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by comparison with a standard of known concentration.
Antibody	Rabbit Polyclonal	Rabbit Polyclonal
Reportable Range	Initial: 0.23 to 8.0 mg/L	0.23 to 8.0 mg/L
Calibrator	N Protein Standard UY (sold separately)	Dimension Vista™ Protein 3 Calibrator (sold separately)
Form	Lyophilized, polygeline based product with urinary proteins of human origin.	Lyophilized, polygeline based product with urinary proteins of human origin.
Constituents	α ₁ - Microglobulin and cystatin C	Albumin and cystatin C
Traceable to	Highly purified proteins	ERM® - DA470 (CRM 470) and Highly purified proteins
Levels	1	1

Control	N Cystatin C Control Level 1 and 2 (included in kit)	Dimension Vista™ Cystatin C Control L and H (sold separately)
Form	Lyophilized, polygeline based product with urinary proteins of human origin	Lyophilized, polygeline based product with urinary proteins of human origin
Constituents	Cystatin C	Cystatin C
Traceable to	Highly purified proteins	ERM® - DA470 (CRM 470) and Highly purified proteins
Levels	1 and 2	L and H
Analyzer	BN™ Systems	Dimension Vista® System

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

STANDARDS
Title and Reference Number
EP5-A Evaluation of Precision Performance of Clinical Chemistry; Approved Guideline (1999).
EP7-P Interference Testing in Clinical Chemistry; Proposed Guideline (1986).
EP9-A Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (1995)

L. Test Principle:

Polystyrene particles coated with specific antibodies to human cystatin C are aggregated when mixed with samples containing human cystatin C. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by comparison with a standard of known concentration.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision studies were done in accordance with CLSI/NCCLS Approved Guideline for Evaluation of Precision Performance of Clinical Devices:

EP5A2. Precision of the system was demonstrated by assaying the low and high kit controls, low, medium and high serum pool specimens, and low and high plasma pool specimens for the Dimension Vista™ CYSC Assay. Specimens at each level were analyzed in duplicate, twice a day, for 20 days (n = 80). The repeatability and within-lab standard deviation (SD) and percent coefficient of variation (%CV) were calculated by the analysis of variance method. The data are summarized below:

CYSC Precision Data Summary

Material	Mean mg/L	Repeatability SD (%CV)	Within-Lab SD (%CV)	Sponsor Acceptable SD Maximum mg/L
CYSC CON L	1.04	0.03 (2.87)	0.04 (3.69)	0.161
CYSC CON M	2.05	0.05 (2.25)	0.07 (3.35)	0.288
Serum Pool low	0.98	0.02 (2.44)	0.04 (3.53)	0.145
Serum Pool med	1.85	0.04 (2.13)	0.06 (3.29)	0.255
Serum Pool high	6.76	0.17 (2.45)	0.28 (4.15)	1.175
Plasma Pool low	0.94	0.03 (2.67)	0.03 (3.46)	0.137
Plasma Pool high	1.71	0.04 (2.06)	0.05 (2.82)	0.202

Precision met the sponsor’s established Acceptable SD maximum presented in the above table:

b. Linearity/assay reportable range:

The measuring range is 0.23 to 8.0 mg/L. Linearity across the assay range was confirmed by testing a calibrator with a high concentration of cystatin C. This calibrator was serially diluted with System diluent (8.75 to 0.16 mg/L). Each dilution was tested in replicates of three. Data were analyzed using linear regression analysis. The sponsor’s acceptance criteria of a slope between 0.9 and 1.1 and a correlation coefficient ≥ 0.95 were met. A summary of the linearity data is presented the table below.

Dimension Vista™	N	Slope	Intercept	Correlation Coefficient
CYSC	6	1.018	0.014	0.999

Hook Effect:

The possibility of hook effect occurring when using the Dimension Vista™ CYSC assay was evaluated by the sponsor with serum samples above the assay range. The samples were analyzed on both the predicate BN ProSpec® System and the Dimension Vista® System, indicating no hook affect up to 13.9 mg/L. The summary of the hook effect data are presented below.

Summary of Hood Effect

BN ProSpec® System Cystatin C Concentration (mg/L)	Dimension Vista® Test Dilution	Dimension Vista® CYSC Concentration (mg/L)
15.00	1:100	>8
	1:1000	13.9

No prozone effect was observed up to at least 13.9 mg/L.

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

The traceability of the calibrators and controls are referenced to ERM® - DA470 (CRM 470) and highly purified proteins with value assignment of the commercial lot versus master calibrator or control. Three reference curves, 4 runs, 3 vials, 4 replicates per vial tested on two nephelometric instruments for a total of 144 values.

Protein 3 Calibrator Stability:

The Protein 3 Calibrator stability was determined per pre-approved test protocol by Dade Behring. A 24 month study with 3 vials, 3 replicates per vial was performed. The calibrator was stored at +2 to +8°C throughout the testing cycle and tested on day 0 and after 12, 18, and 24 months. Stress testing was performed after storage for 6 months at +2 to +8°C; the calibrator was stored at +37°C for 2 weeks and tested after 1 and 2 weeks storage. Open and punctured vial stability was tested after having reached 50% of shelf life stability, vials were stored on board the instrument and contents were tested in duplicates on day 0, 4, 7, 9, 11, and 14. The sponsor's established shelf life stability criteria are results obtained must be within a range of 85 to 115% of the control assigned value. The sponsor's established open and punctured vial stability criteria are results obtained must not deviate more than ± 10% compared to day 0 results.

Cystatin C Control L and H Stability:

The Cystatin C Control L and H stability was determined per pre-approved test protocol by Dade Behring. A 24 month study with 3 vials, 3 replicates per vial was performed. The controls were stored at +2 to +8°C throughout the testing cycle and tested on day 0 and after 12, 18, and 24 months. Stress testing was performed after storage for 6 months at +2 to +8°C; the controls were stored at +37°C for 2 weeks and tested after 1 and 2 weeks storage. Open and punctured vial stability was tested after having reached 50% of shelf life stability, vials were stored on board the instrument and contents were tested in duplicates on day 0, 4, 7, 9, 11, and 14. The sponsor's established shelf life stability criteria are results obtained must be within a range of 85 to 115% of the control assigned value. The sponsor's established open and punctured vial stability

criteria are results obtained must not deviate more than $\pm 10\%$ compared to day 0 results.

d. Detection limit:

The sponsor defined analytical sensitivity as the minimal detectable level of analyte, which can be distinguished from zero. In a representative study the value was calculated as the mean value of twenty replicates of System Diluent plus two standard deviations. In this study, the mean analytical sensitivity was calculated as 0.0038 mg/L. The claimed low end of assay range is 0.23 mg/L.

e. Analytical specificity:

The sponsor conducted interference studies to evaluate the effect of various endogenous and exogenous substances on the Dimension Vista™ CYSC assay. Interference testing was performed according to CLSI/NCCLS EP7-A. The sponsors established acceptance criteria are a bias exceeding $\pm 10\%$ was considered a significant interference. For each spiked sample, the % recovery was determined [% Recovery = (Test result/ Baseline) x 100]. The acceptance criterion of $\pm 10\%$ relative deviation from the base pool was met for all interferents tested. The results are presented in the table below.

Substance	Concentration	Cystatin C concentration	Bias in %
Hemoglobin (hemolysate)	1000 mg/dL	0.94 mg/L	+3
Bilirubin (unconjugated)	60 mg/dL	0.93 mg/L	+2
Bilirubin (conjugated)	60 mg/dL	0.93 mg/L	+1
Lipemia (triglycerides)	1071 mg/dL	0.83 mg/L	-4

Method comparison studies were run on BN ProSpec® (BNPS) versus the Dimension Vista® System, to determine total protein and rheumatoid factor interference. For these studies serum sample preparations ($n \geq 25$) with 12 g/dL (120 g/L) protein and 500 IU/mL RF were used. The median for the normalized difference in % was required to be within $\pm 7\%$ and the correlation coefficient ≥ 0.95 . These studies demonstrated correlation and equivalent performance between the Dade Behring N Latex Cystatin C Kit and the Dimension Vista™ CYSC assay.

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

A study was performed comparing the Dimension Vista™ CYSC assay to the Dade Behring N Latex Cystatin C Kit on the BN ProSpec® System by evaluating serum and plasma samples with concentrations ranging from 0.33 to 7.46 mg/L. Regression analysis of these results yielded the following equation.

Method Comparison Study

Comparative Method	N	Slope	Intercept mg/L	Correlation Coefficient
N Latex Cystatin C on the BN ProSpec®	160	1.005	0.005	0.998

Pooled evaluation:

Serum n = 78

Plasma n = 82

n = 160 (pooled)

$$y = 1.0053 x + 0.0054$$

95% - Confidence Interval:

Slope (1.0000, 1.0244)

Intercept (-0.0121, 0.0100)

Pearson correlation coefficient:

$$R = 0.9981 \quad (r^2 = 0.9962)$$

b. Matrix comparison:

Serum EDTA plasma or heparinized plasma are the recommended specimens for the Dimension Vista™ CYSC assay. A comparison study was performed with matched specimens of serum, and EDTA, lithium heparin, and sodium heparin plasma ranging from 0.34 to 7.71 mg/L, assayed on the Dimension Vista™ System. Linear regression analyses demonstrated agreement between the serum and plasma samples as follows:

	Li heparin	Na heparin	EDTA
Slope – (95% CI)	1.02 (0.981-1.06)	1.06 (1.018-1.10)	1.05 (1.023-1.07)
Y – intercept	-0.04	-0.10	-0.09
r	0.997	0.998	0.999
Syx	0.19	0.17	0.11
% recovery mean	0.3%	1.8%	0.4%
% recovery min	-3.5%	-3.7%	-5.9%
% recovery max	7.2%	9.2%	6.5%

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):

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Expected Values: 0.53 – 0.95 mg/L

The reference interval was determined from a population of apparently subjects with no history of renal disease. A total of 413 samples obtained from 194 males and 219 females ranging in age from 1 to 78 years were tested. The reference interval was calculated nonparametrically and was determined to be 0.53 – 0.95 mg/L.

In the labeling the sponsor recommends that each laboratory should establish its own expected values for cystatin C as performed on the Dimension Vista® System.

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.