

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY

A. 510(k) Number:

k083463

B. Purpose for Submission:

Device modification (addition of urine matrix)

C. Measurand:

β_2 -microglobulin

D. Type of Test:

Quantitative, immunonephelometry

E. Applicant:

Seimens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Dimension Vista® B2MIC Flex ® reagent cartridge

Dimension Vista® Protein 1 Calibrator

Dimension Vista® Protein 1 Control L

Dimension Vista® Protein 1 Control M

G. Regulatory Information:

1. Regulation section:

866.5630 Beta-2-microglobulin immunological test system

862.1150 Calibrator

862.1660 Quality Control Material (Assayed and Unassayed)

2. Classification:

Class II

3. Product code:

JZG System, test, beta-2-microglobulin immunological

JIX Calibrator, multi-analyte mixture

JJY Multi-analyte controls, all kinds (assayed)

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

Dimension Vista® B2MIC Flex ® reagent cartridge: The B2MIC method is an in vitro diagnostic test for the quantitative measurement of β_2 -microglobulin in human serum, heparinized plasma, EDTA plasma, and urine using on the Dimension Vista® Systems. Measurement of β_2 -microglobulin aids in the diagnosis of active rheumatoid arthritis and kidney disease.

Dimension Vista® Protein 1 Calibrator: PROT1 CAL is an in vitro diagnostic product for the calibration of the Dimension Vista® Systems for: α_1 -acid glycoprotein, α_1 -antitrypsin, α_2 -macroglobulin, β_2 -microglobulin, C3 complement, C4 complement, ceruloplasmin, haptoglobin, hemopexin, immunoglobulin A, immunoglobulin E, immunoglobulin G, immunoglobulin G subclass 1, immunoglobulin G subclass 2, immunoglobulin G subclass 3, immunoglobulin G subclass 4, immunoglobulin M, prealbumin, retinol binding

protein, homocysteine, soluble transferrin receptor and transferrin.

Dimension Vista® Protein 1 Control L: PROT1 CON L is an assayed, low level, intra-laboratory quality control for assessment of precision and analytical bias on the Dimension Vista® Systems in the quantitative determination of: α 1-acid glycoprotein, α 1-antitrypsin, α 2-macroglobulin, β 2-microglobulin, C3 complement, C4 complement, ceruloplasmin, haptoglobin, hemopexin, immunoglobulin E, immunoglobulin A, immunoglobulin G, immunoglobulin G Subclass, immunoglobulin G subclass 2, immunoglobulin G subclass 3, immunoglobulin G subclass 4, immunoglobulin M, prealbumin, retinol binding protein, homocysteine, soluble transferrin receptor and transferrin.

Dimension Vista® Protein 1 Control M: PROT1 CON M is an assayed, mid-level, intra-laboratory quality controls for assessment of precision and analytical bias on the Dimension Vista® System in the quantitative determination of: α 1-acid glycoprotein, α 1-antitrypsin, α 2-macroglobulin, β 2-microglobulin, C3 complement, C4 complement, ceruloplasmin, haptoglobin, hemopexin, immunoglobulin E, immunoglobulin A, immunoglobulin G, immunoglobulin G Subclass, immunoglobulin G subclass 2, immunoglobulin G subclass 3, immunoglobulin G subclass 4, immunoglobulin M, prealbumin, retinol binding protein, homocysteine, soluble transferrin receptor and transferrin.

2. Indication(s) for use:
Same as above.
3. Special conditions for use statement(s):
For prescription use only
4. Special instrument requirements:
Dimension Vista® System

I. Device Description:

Dimension Vista® B2MIC Flex® reagent cartridge: The cartridge consists of 12 wells capable of providing 100 test results (2 cartridges per carton). All wells contain preservative. Reagent 1 (phosphate buffer, polyethylene glycol sorbitan monolaureate), Reagent 2 (phosphate buffer and immunoglobulin) and a third Reagent consisting of polystyrene particles and monoclonal antibodies to human β 2-microglobulin. The carton is also supplied with 2 vials of urine stabilizer (polyethylene glycol sorbitan monolaureate solution). Reagents are ready-to-use.

Dimension Vista® Protein 1 Calibrator: Protein 1 calibrator is a multi-analyte, liquid human serum based product in a ready-to-use form supplied as 6 vials, 2.0 ml per vial.

Dimension Vista® Protein 1 Control L and Protein 1 Control M: Protein 1 Control L and M are multi-analyte, low and mid level, ready-to-use liquid human serum based products. Supplied as 6 vials, 2.0 ml per vial.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) numbers:

N Latex β 2-microglobulin	k002731
N/T Protein Standard SL	k052788
N Protein Controls SL	k052788

2. Comparison with predicate:

B2MIC Flex® reagent cartridge

Similarities		
Item	New Device	Predicate
Intended Use/Indications for Use	For the quantitative measurement of β 2-microglobulin in human serum, heparinized plasma, EDTA plasma and urine. Measurements of β 2-microglobulin aid in the diagnosis of active rheumatoid arthritis and kidney disease.	Same
Technology	Immunonephelometry	Same
Sample types	Serum, heparinized plasma, (Li & Na), EDTA plasma, and urine	Same
Antibody	Mouse monoclonal	Same
Reagent preparation	Liquid and ready for use	Same
Storage	Unopened 2-8°C	Same

Differences		
Item	New Device	Predicate
Analyzer	Dimension Vista Systems	BN TM Systems
Reportable range	0.20 – 5.80 mg/L (0.02 – 0.58 mg/dL)	0.20 – 6.0 mg/L
Stability: Open well	21 days at 2-8°C	4 weeks at 2-8°C

PROT 1 Controls L and M

Similarities		
Item	New Device	Predicate
Intended Use	PROT 1 CON L and M are assayed, low level and mid-level intra-laboratory quality control for the assessment of precision and analytical bias	Same
Material Source	Human Serum	Same
Reagent Preparation	Ready-to-Use	Same

Differences		
Item	New Device	Predicate
Instrument System	Dimension Vista	BN Systems
Analytes	α 1-acid glycoprotein, α 1-antitrypsin, α 2-macroglobulin, β 2-microglobulin, C3	α 1-acid glycoprotein, α 1-antitrypsin, α 2-macroglobulin, β 2 –

Differences		
Item	New Device	Predicate
	complement, C4 complement, ceruloplasmin, haptoglobin, hemopexin, immunoglobulins A, E, G and M, IgG subclass 1 to subclass 4, light chains kappa, light chains lambda, prealbumin, retinol binding protein, homocysteine, soluble transferrin receptor and transferrin, Immunoglobulin E (IgE)	microglobulin, C3 complement, C4 complement, ceruloplasmin, haptoglobin, hemopexin, immunoglobulins A, E, G and M, IgG subclass 1 to subclass 4, light chains kappa, light chains lambda, prealbumin, retinol binding protein, transferrin, albumin, soluble transferrin receptor, ferritin, and total protein
Levels	Low and Medium	Low, Medium and High
Stability; Open	9 days at 2-8°C	14 days at 2-8°C
Quantity	6 vials, 2.0 mL per vial	3 vials, 1 mL per vial

PROT1 Calibrator

Similarities		
Item	New Device	Predicate
Intended Use	An in vitro diagnostic product for the calibration of specific analytes	Establishment of reference curves for specific analytes
Traceability for TRF- U	WHO 1 st International Standard for β 2-microglobulin	Same
Composition	Liquid human serum based	Same
Levels	1 level diluted with System Diluent to 6 levels. Approximate concentrations: 0.01, 0.02, 0.04, 0.07, 0.15, 0.39 mg/L)	1 level serially diluted
Reagent Preparation	Ready-to-Use	Same
Stability; Open	14 days at 2-8°C	Same
Storage	2-8°C	Same

Differences		
Item	New Device	Predicate
Analytes	α 1-acid glycoprotein, α 1- antitrypsin, α 2-macroglobulin, β 2-microglobulin, C3 complement, C4 complement,	α 1-acid glycoprotein, α 1-antitrypsin α 2- macroglobulin, β 2 – microglobulin, C3

Differences		
Item	New Device	Predicate
	ceruloplasmin, haptoglobin, hemopexin, immunoglobulins A, E, G, and M, IgG subclass 1 to subclass 4, light chains kappa, light chains lambda, prealbumin, retinol binding protein, homocysteine, soluble transferrin receptor and transferrin, Immunoglobulin E (IgE).	complement, C4 complement, ceruloplasmin, haptoglobin, hemopexin, immunoglobulins A, E, G and M, IgG subclass 1 to subclass 4, light chains kappa, light chains lambda, prealbumin, retinol binding protein, transferrin, albumin, soluble transferrin receptor, ferritin, and total protein
Quantity	4 vials, 1.0 mL per vial	3 vials, 1 mL per vial

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

Guidance for Industry and FDA Staff- Assayed and Unassayed Quality Control Material.

CLSI EP5-A2: Evaluation of Precision Performance in Clinical Chemistry Devices.

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.

CLSI EP7-A2 Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition.

L. Test Principle:

Proteins contained in human body fluids form immune complexes in an immunochemical reaction with specific antibodies. These complexes scatter a beam of light passed through the sample. The intensity of the scattered light at 840 nm is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration.

M. Performance Characteristics (if/when applicable):

The performance characteristics for β_2 -microglobulin in serum and plasma are available in the Decision Summary for k063272. The evaluation of β_2 -microglobulin in urine is referred to as the B2MU method below.

1. Analytical performance:

- a. *Precision/Reproducibility:* Precision testing for the B2MU method was conducted over twenty days according to CLSI/NCCLS EP5-A2, at a single site. A single instrument, a single reagent lot and a single operator were used. On each day of testing, each sample was run in duplicate in two separate runs. The test samples consisted of two levels of Dimension Vista® Protein 1 Controls, and two pooled urine samples that covered the low and high ends of

the measuring range. Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of EP5-A2. The % CVs for the controls was less than 2.35% and the % CV for the urine pools was less than 6.7%. The data are shown below:

Sample	n	Mean		Repeatability			Within-Lab		
		mg/dL	mg/L	SD mg/dL	SD mg/L	%CV	SD mg/dL	mg/L	%CV
PROT1 CON L	80	0.11	1.12	0.002	0.019	1.75	0.003	0.026	2.35
PROT1 CON M	80	0.019	1.86	0.004	0.036	1.93	0.004	0.04	2.15
Urine pool	80	0.071	0.71	0.002	0.021	2.92	0.005	0.048	6.66
Urine pool	80	0.45	4.48	0.17	0.169	3.78	0.028	0.276	6.15

Lot-to-Lot precision was demonstrated using four samples covering the assay range and testing on three reagent lots. Each sample was assayed in triplicate from three different Flex® cartridges, producing nine replicates per sample for each of the three reagent lots. The mean, standard deviation and % CV was calculated for the data set of each sample from each lot. The % CV values were then used to determine the mean % CV and standard deviation across lots. For each sample, a one sided 95% confidence interval was used to determine the upper limit. The acceptance limit for % CV for lot-to-lot precision of < 5% was met.

b. *Linearity/assay reportable range:*

The reportable range for the B2MU method was determined according to CLSI EP-6-A. A high urine sample (5.95 mg/L) was diluted with System diluent. A urine sample was run neat along with serial dilutions to cover the assay range. A total of 13 levels were prepared and tested. The observed value represents the mean of five replicates. Per the EP6-A procedure, the observed (Y-axis) and expected (X-axis) values were fit by linear and cubic models. Weighted regression fits were used for both models. The same weighting factors were used for each model and were derived from the replicates data by the classical approach of 1/Variance. These models were used to generate predicted values for each sample. The difference between the linear and cubic predicted values for each sample was taken as the bias at each level. The acceptance criteria were defined as: Bias at each level $\leq \pm 0.05$ mg/L or 15%, and the mean bias for all levels $\leq \pm 15\%$. The range of the bias was -4.98 to +5.08 % (-0.13 to +0.05 mg/L), the mean absolute bias was 2.8 %. The acceptance criteria were met. The BSMU analytical measuring range is 0.20 – 5.80 mg/L (0.02 – 0.58 mg/dL). The first order polynomial is used for the best fitting straight line (linear fit). The regression analysis for the linear fit is as follows: Slope = 0.965 Intercept = 0.029. The range of percent recovery at each concentration (observed value/target value) is shown below:

Sample	Expected mg/L	Recovery Range (%)
1	0.00	100
2	0.13	100-107
3	0.31	103-106
4	0.50	102
5	0.63	102-103
6	1.25	102-103
7	1.88	102-103
8	2.51	102
9	3.13	103
10	3.76	103
11	4.39	108-110
12	5.01	103-104
13	5.64	102-104
14	6.27	101-102

- c. *Hook Effect*: The possibility of hook effect occurring when using the B2MU assay was evaluated. Testing indicated no hook effect up to 24.4 mg/dL (244 mg/L).
- d. *Traceability, Stability, Expected values (controls, calibrators)*:
The calibrator and control are traceable to WHO 1st International Preparation for β_2 -microglobulin.

Stability: Material was tested at day 0, and after 12, 18 and 24 months. Three vials, 3 replicates per vial were tested. For open vial stability, vials were stored on board the instrument and tested in duplicate at 0, 4, 7, 9, 11, 14 days. The acceptance criteria for shelf life ($\pm 15\%$ of the assigned value) and open vial ($\pm 10\%$ of the day 0 value) were met.

Calibrator Expected Values: A typical assigned value for β_2 -microglobulin, in Dimension Vista® Protein 1 Calibrator is 0.116 mg/dL (1.16 mg/L). Calibration is required for any new lot of reagent or every 30 days for the same lot.

Control Expected Values: A typical analyte concentration for β_2 -microglobulin in Protein 1 Control L is 0.112 mg/dL (1.12 mg/L), and for β_2 -microglobulin in Protein 1 Control M is 0.186 mg/dL (1.86 mg/L).

- e. *Detection limit*:
Limit of Quantification: Three human urine samples were spiked with the 1st International Standard for β_2 -microglobulin concentration of 0.19 mg/L. Five

runs of triplicate determinations on each of three human urine samples were tested on one day with a single reagent and a calibrator lot and instrument. The mean and SD for the 15 replicates for each sample were calculated. The bias for each sample was determined (bias = mean - sample determination). The average bias across the three samples for each concentration was calculated. The pooled SD across the three samples was determined per EP17-A Appendix B. The observed Total Analytical Error (TAE) was calculated. (TAE = average bias plus 2SD) Limit of Quantitation (LoQ) was determined based on the TAE. An acceptance criterion of 30% was used based on precision and recovery performance of the method. The Limit of Quantitation for β_2 -microglobulin in urine was determined to be 0.019 mg/dL (0.19 mg/L).

f. *Analytical specificity:*

Interference testing was conducted in accordance with CLSI EP7-A2 Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition. Test samples were prepared by spiking the potential interferent into urine. Ten replicates of each urine sample with interferent were tested. Control samples for β_2 -microglobulin in the urine samples tested ranged from 0.022 mg/dL - 0.495mg/dL (0.22 mg/L - 4.95 mg/L). The recovery of β_2 -microglobulin in the presence of spiked material ranged from 90 - 103 %. The acceptance criterion for the bias (less than $\pm 10\%$) was met in all cases.

Interferent	Concentration spiked
Acetone	1000 mg/dL
Ascorbic acid	750 mg/dL
Boric acid	800 mg/dL
Creatinine	500 mg/dL
Ethanol	1000 mg/dL
Glucose	2000 mg/dL
Human serum albumin	500 mg/dL
Immunoglobulin G (IgG)	500 mg/dL
Oxalic acid	100 mg/dL
Riboflavin	7.5 mg/dL
Sodium azide	1000 mg/dL
Sodium chloride	6000 mg/dL
Sodium fluoride	900 mg/dL
Urea	4000 mg/dL

g. *Assay cut-off:*

The concentration of β_2 -microglobulin in urine of healthy individuals is below the detection limit of detection for this method (less than 0.020 mg/dL [0.20 mg/L]). Samples with less than 0.02 mg/dL (0.20 mg/L) are reported as “less than 0.02 mg/dL” by the instrument.

2. Comparison studies:

a. *Method comparison with predicate device:*

Performance between the Dimension Vista® B2MIC Flex® reagent cartridge and the predicate was compared. The study included 42 native specimens, with β_2 -microglobulin ranging from 0.022 - 0.55 mg/dL (0.22 - 5.52 mg/L), and 40 spiked specimens. Spiked samples were prepared by adding purified β_2 -microglobulin to individual specimens. An additional 27 samples were run for the extended high range. Passing-Bablok regression yielded the following statistics:

Comparative Method	Sample range (mg/L)	Slope (mg/L) (95%CI)	Y-Intercept (mg/L) (95%CI)	Correlation Coefficient (r ²)	n
N Latex β_2 -microglobulin on the BN ProSpec® System	0.22 - 5.52	0.952 (0.926 to 0.972)	0.008 (-0.023 to 0.018)	0.975	82
	9.26 - 21.0	0.971 (0.866 to 1.089)	0.653 (-0.603 to 1.807)	0.907	33

b. *Matrix comparison:*

Not applicable

3. Clinical studies:

a. *Clinical Sensitivity and Specificity:*

Not applicable.

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

Not applicable.

4. Clinical cut-off:

Same as assay cut-off.

5. Expected values/Reference range:

The concentration of β_2 -microglobulin in urine of healthy individuals is below the detection limit of detection for this method (less than 0.020 mg/dL [0.20 mg/L]). This reference interval is based on Lammers M, Gentzler W., Reifferscheidt G, Schmidt B. Determination of Beta 2 microglobulin by a particle enhanced immunonephelometric assay. Clin Chem 2002; 48: A-119. The reference interval was confirmed by running a transference study as outlined in CLSI C28-A2 How to Define and Determine Reference Intervals in the Clinical Laboratory - Second Edition. The acceptance criterion was defined that no more than 10% of the values could lie outside the published range of < 0.02 mg/dL. The acceptance criterion was met as all samples fell within the published range.

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.