510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k081249

B. Purpose for Submission:
New analyte, controls, and calibrator

C. Measurand:
Alpha 2 macroglobulin

D. Type of Test:
Quantitative, Nephelometric

E. Applicant:
Dade Behring, Inc.

F. Proprietary and Established Names:
Dimension Vista System A2mac Flex Reagent Cartridge, Dimension Vista System Protein 1 Calibrator, Dimension Vista System.

G. Regulatory Information:

Regulation Section	Classification	Product Code	Panel
21 CFR 866.5620, Alpha-2-macroglobulin immunological test system.	Class II	Alpha-2-Macroglobulin, Antigen, Antiserum, Control (DEB)	82 Immunology (IM)
21 CFR 862.1660, Quality control material (assayed and unassayed).	Class I	Multi-Analyte Controls, All Kinds (Assayed) (JJY)	75 Clinical Chemistry (CH)
21 CFR 862.1150, Calibrator.	Class II	Calibrator, Multi-Analyte Mixture (JIX)	75 Clinical Chemistry (CH)

H. Intended Use:

1. Intended use(s):
   Dimension Vista® System A2MAC Flex® Reagent Cartridge
   The A2MAC assay is an in vitro diagnostic test for the quantitative measurement of alpha2-macroglobulin in human serum and heparinized and EDTA plasma on the Dimension Vista® Systems. Measurements of a2-macroglobulin aid in the diagnosis of blood clotting or blood lysis disorders.

   Dimension Vista® Protein 1 Calibrator
   Dimension Vista® Protein 1 Calibrator is an in vitro diagnostic product for the calibration of the Dimension Vista® System for: α1-Acid Glycoprotein (A1AG), α1-Antitrypsin(A1AT), α2-Macroglobulin (A2MAC), β2-Microglobulin (B2MIC), C3 Complement (C3), C4 Complement (C4), Ceruloplasmin(CER), Haptoglobin (HAPT), Hemopexin (HPX), Homocysteine (HCYS), Immunoglobulin A (IGA), Immunoglobulin E (IGE), Immunoglobulin G (IGG, IGG-C*), Immunoglobulin G Subclass 1, (IGG1), Immunoglobulin G Subclass 2 (IGG2), Immunoglobulin G

Subclass 3 (IGG3), Immunoglobulin Subclass 4 (IGG4), Immunoglobulin M (IGM), Prealbumin (PREALB), Retinol Binding Protein (RBP), soluble Transferrin Receptor (sTFR) and Transferring (TRF).
*for cerebrospinal fluid

Dimension Vista® Protein 1 Control L
Dimension Vista® Protein 1 Control L is an assayed, low level, intra-laboratory control for the assessment of precision and analytical bias on the Dimension Vista®System in the quantitative measurement of: α1-Acid Glycoprotein (A1AG), α1-Antitrypsin(A1AT), α2-Macroglobulin (A2MAC), C3 Complement (C3), C4 Complement (C4), Ceruloplasmin(CER), Haptoglobin (HAPT), Hemopexin (HPX), Homocysteine (HCYS), Immunoglobulin A (IGA), Immunoglobulin E (IGE), Immunoglobulin G (IGG), Immunoglobulin G Subclass 1 (IGG1), Immunoglobulin G Subclass 2 (IGG2), Immunoglobulin G Subclass 3 (IGG3), Immunoglobulin Subclass 4 (IGG4), Immunoglobulin M (IGM), Prealbumin (PREALB), Retinol Binding Protein (RBP), soluble Transferrin Receptor (sTFR), specialty Albumin (sALB*) and Transferring (TRF).
*for serum and plasma

Dimension Vista® Protein 1 Control M
Dimension Vista® Protein 1 Control M is an assayed, mid level, intralaboratory control for the assessment of precision and analytical bias on the Dimension Vista®System in the quantitative measurement of: α1-Acid Glycoprotein (A1AG), α1-Antitrypsin(A1AT), α2-Macroglobulin (A2MAC), β2-Microglobulin (B2MIC), C3 Complement (C3), C4 Complement (C4), Ceruloplasmin(CER), Haptoglobin (HAPT), Hemopexin (HPX), Homocysteine (HCYS), Immunoglobulin A (IGA), Immunoglobulin E (IGE), Immunoglobulin G (IGG), Immunoglobulin G Subclass 1 (IGG1), Immunoglobulin G Subclass 2 (IGG2), Immunoglobulin G Subclass 3 (IGG3), Immunoglobulin Subclass 4 (IGG4), Immunoglobulin M (IGM), Prealbumin (PREALB), Retinol Binding Protein (RBP), soluble Transferrin Receptor (sTFR), specialty Albumin (sALB*) and Transferrin (TRF).
*for serum and plasma

Dimension Vista® Protein 1 Control H
Dimension Vista® Protein 1 Control H is an assayed, high level, intralaboratory control for the assessment of precision and analytical bias on the Dimension Vista®System in the quantitative measurement of: α1-Acid Glycoprotein (A1AG), α1-Antitrypsin(A1AT), α2-Macroglobulin (A2MAC), β2-Microglobulin (B2MIC),C3 Complement (C3), C4 Complement (C4), Ceruloplasmin(CER), Haptoglobin (HAPT), Hemopexin (HPX), Homocysteine (HCYS), Immunoglobulin A (IGA), Immunoglobulin E (IGE), Immunoglobulin G (IGG), Immunoglobulin G Subclass 1, (IGG1), Immunoglobulin G Subclass 2 (IGG2), Immunoglobulin G Subclass 3 (IGG3), Immunoglobulin Subclass 4 (IGG4), Immunoglobulin M (IGM), Prealbumin (PREALB), Retinol Binding Protein (RBP), soluble Transferrin Receptor (sTFR), specialty Albumin (sALB*) and Transferring (TRF).

*for serum and plasma

2. Indication(s) for use:
   Same as Intended use
3. Special conditions for use statement(s):
   For Prescription use only.
4. Special instrument requirements:
   The Dimension Vista® A2MAC Flex® Reagent Cartridge, the Dimension Vista Protein 1 Calibrator, and Dimension Vista Protein 1 Control L, M, and H are for use on the Dimension Vista System, previously cleared under k051087, and its family member, Dimension Vista System 3000T.

I. Device Description:

The assay is supplied as a liquid, ready-to-use single reagent kit containing Arsenazo-III dye at a concentration of 0.2 mmol/L. Reagents are contained in 12 segregated wells in a plastic cartridge. Wells 1 - 8 contain buffers and polyethylene glycol. Wells 9 - 12 contain liquid rabbit antiserum to human α2-macroglobulin. There are two Flex® reagent cartridges per carton.

PROT1 CAL is a multi-analyte, liquid human based product.

PROT1 CON L, M and H are multi-analyte liquid human serum based product with low, medium and high levels respectively.

All human materials included in the calibrators and controls were tested by FDA approved methods and found to be negative for the presence of antibodies to HIV-1, HIV-2, HBsAg, and HCV.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   N Antiserum to Human alpha 2 Macroglobulin
   N Protein Standard SL
   N/T Protein Controls SL L, M, and H
2. Predicate 510(k) number(s):
   k053073, k860894
   k012470
   k012468
3. Comparison with predicate:

Feature	N Antisera to Human α_2-Macroglobulin (Predicate)	Dimension Vista® A2MAC Assay (New assay)
Similarities:		
Intended Use:	*In vitro* diagnostic reagents for the quantitative determination of α_2-macroglobulin in human plasma and serum	Same.
Technology:	Nephelometry	Same
Antibody:	Rabbit Polyclonal	Same
Reagents	Reagents are liquid and ready for use	Same

Differences:		
Analyzer:	BN™ Systems	Dimension Vista® Systems

Feature	N Protein Standard SL	Dimension Vista® PROT 1 CAL
Similarities:		
Intended Use:	For the calibration of the α_2-macroglobulin method.	Same
Form:	Liquid human serum based.	Same
Traceability	All analytes in N Protein Standard SL are traceable to recognized standards or highly purified proteins for all components. Values for α_2-macroglobulin are traceable to ERM®DA 470 (CRM470).	Same
Differences:		
Instruments:	BN™ Systems.	Dimension Vista® Systems.
Constituents:	N Protein Standard SL contains: α_1-acid glycoprotein, α_1-antrypsin, albumin, α_2 – macroglobulin, β_2-microglobulin, C_3 Complement, C_4 complement, ceruloplasmin, ferritin, haptoglobin, hemopexin, homocysteine, IgA, IgE, IgG, IgG1, IgG2, IgG3, IgG4, immunoglobulin light chains kappa, immunoglobulin light chains lambda, IgM, prealbumin, retinol binding protein, total protein, soluble transferrin receptor and transferrin.	Dimension Vista® PROT 1 CAL contains: α_1-acid glycoprotein, α_1-antrypsin, α_2 – macroglobulin, β_2-microglobulin, C_3 complement, C_4 complement, ceruloplasmin, haptoglobin, hemopexin, homocysteine, IgA, IgE, IgG, IgG1, IgG2, IgG3, IgG4, IgM, prealbumin, retinol binding protein, soluble transferrin receptor and transferrin.

Feature	N/T Protein Controls SL	Dimension Vista® PROT 1 CON
Similarities:		
Intended Use:	Assayed interlaboratory controls for the assessment of precision and analytical bias on automated systems.	Same
Form:	Liquid, human based material ready for use.	Same
Differences:		
Instruments:	BN™ Systems.	Dimension Vista Systems.
Constituents	N Protein Controls SL L, M and H are low, mid and high level controls respectively. They are multianalyte controls containing α_1-acid glycoprotein, α_1-antrypsin, α_2 – macroglobulin, albumin, β_2-microglobulin, C_3 Complement, C_4 complement, ceruloplasmin, haptoglobin, hemopexin, ferritin, IgA, IgE, IgG, IgG1, 2, 3 and 4 immunoglobulin/light chains kappa, immunoglobulin/light chains lambda,	Dimension Vista® PROT 1 CON L, is a low level multianalyte control containing: α_1-antrypsin, α_2 – macroglobulin, albumin, C_3 Complement, C_4 complement, ceruloplasmin, haptoglobin, hemopexin, homocysteine, IgA, IgE, IgG, IgG1, 2, 3 and 4, IgM, prealbumin, retinol binding protein, soluble transferrin receptor and transferrin.

Feature	N/T Protein Controls SL	Dimension Vista® PROT 1 CON
	IgM, prealbumin, retinol binding protein, soluble transferrin receptor, total protein and transferrin.	Dimension Vista® PROT 1 CON M and H are mid and high level controls respectively containing: α_1-acid glycoprotein, α_1-antrypsin, α_2 – macroglobulin, albumin, β_2-microglobulin, C_3 Complement, C_4 complement, ceruloplasmin, haptoglobin, hemopexin, IgA, IgE, IgG, IgG1, 2, 3 and 4, immunoglobulin/ light chains kappa, immunoglobulin/light chains lambda, IgM, prealbumin, retinol binding protein, soluble transferrin receptor and transferrin.

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

GUIDANCE			
Document Title	**Office**	**Division**	**Web Page**
Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material			**http://www.fda.gov/cdrh/oivd/guidance/2231.html**

L. Test Principle:

The Dimension Vista® A2MAC method is based on the principle of nephelometry. 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 and the scattered light is measured. The intensity of the scattered light is proportional to the concentration of the respective protein in the sample. The result is evaluated by comparison with a standard of known concentration. The principle of nephelometry is used by the device as well as the predicate.

The Dimension Vista® A2MAC method uses antisera to human a_2 -macroglobulin which is produced by immunization of rabbits with highly purified human a_2-macroglobulin.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. *Precision/Reproducibility:*
   This study was done over twenty days according to CLSI/NCCLS EP5-A2, at a single site using a single instrument, a single reagent lot and two operators. On each day of testing, each sample was run in duplicate, in two separate runs. The test samples consisted of three levels of Dimension Vista ® Protein 1 Controls, two serum samples and two plasma samples.

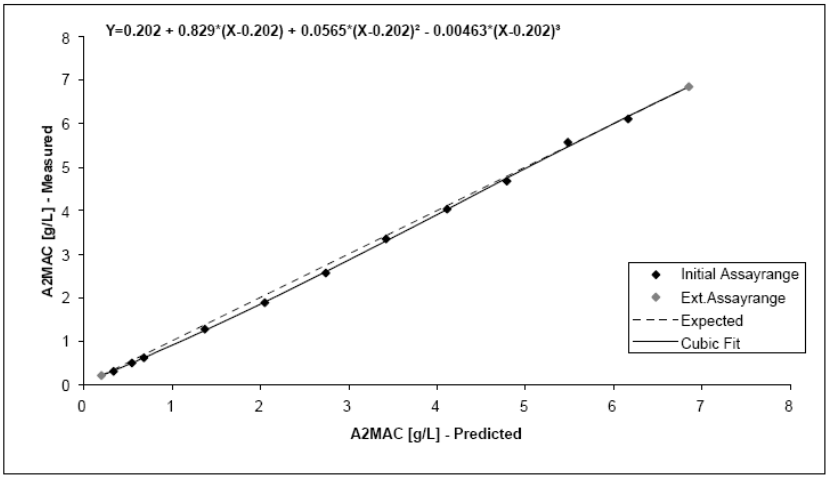
The pools were established at levels below the expected range, at low and high points in the expected range and at a level at the upper portion of the analytical measuring range. The serum and plasma pools with high concentrations were prepared by spiking a native pool with purified analyte.

Analysis of variance (ANOVA) was used to evaluate the data consistent with the recommendations of EP5-A2.

Material	Mean mg/dL [g/L]		Standard Deviation mg/dL [g/L] (% CV) Repeatability Within-Lab					
PROT1 CON L	123	[1.23]	2	[0.02]	(1.8)	3	[0.03]	(2.6)
PROT1 CON M	142	[1.42]	2	[0.02]	(1.7)	3	[0.03]	(2.4)
PROT1 CON H	224	[2.24]	5	[0.05]	(2.0)	7	[0.07]	(3.0)
Serum pool	103	[1.03]	2	[0.02]	(1.6)	3	[0.03]	(2.9)
Serum pool	591	[5.91]	12	[0.12]	(2.1)	18	[0.18]	(3.1)
Plasma pool	151	[1.51]	2	[0.02]	(1.5)	4	[0.04]	(2.5)
Plasma pool	271	[2.71]	5	[0.05]	(1.9)	7	[0.07]	(2.5)

b. Linearity/assay reportable range:
The A2MAC measuring range is 27 - 640 mg/dL (0.27 - 6.4 g/L).

The linear range was determined according to CLSI, EP06-A. The linearity study covered a range of 20.2 to 685 mg/dL (0.202 - 6.85 g/L). The linearity studies were performed using a high serum sample (685 mg/dL). Serial dilutions were prepared using System Diluent. Based on the results of this testing and that from the Limit of Quantitation Study, the measuring range was established.



c. Traceability, Stability, Expected values (controls, calibrators, or methods):
The calibrator and Protein 1 Control L, M, and H are traceable to ERM®-DA470 (CRM470).

d. Detection limit:

Three human serum samples were spiked with ERM® -DA470 with a known concentration of α2-macroglobulin. Two concentrations were tested, 270 mg/dL (0.27 g/L) and 70 mg/dL (0.07 g/L). These levels were chosen to challenge the low end of the analytical measuring range (1:20) and extended low range (1:5) of the assay.

Five runs of triplicate determinations on each of three human serum samples were tested on one day with a single reagent and calibrator lot and a single instrument and operator.

The Limit of Quantitation was determined to be 6.8 mg/dL (0.068 g/L) using the calculations described in CLSA Guideline EP17-A.

e. Analytical specificity:

Test samples were prepared by spiking the potential interferent into serum except for rheumatoid factors. CLSI/NCCLS EP7-A2 was followed to select the intereferent level.

The concentration of α2-macroglobulin in the serum samples tested ranged from 118 mg/dL - 392 mg/dL (1.18 g/L - 3.92 g/L).

Ten replicates of each serum sample with interferent were tested. All samples that were tested for interference, except RF, were compared to a negative control or baseline samples without the spiking material. Interference was defined as "recovery" of a2-macroglobulin greater than ±10% of the baseline sample. Recovery of a2-macroglobulin was in the range of 97 - 110% when compared to the sample without the interfering compound. The acceptance criterion for the bias (</= 10%) was met in all cases.

Substance	Test Concentration	SI Units
Acetaminophen	20 mg/dL	1328 µmol/L
Amikacin	15 mg/dL	256 µmol/L
Ammonium heparin	3 U/mL	3000 U/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic acid	5 mg/dL	284 µmol/L
Caffeine	6 mg/dL	308 µmol/L
Carbamazepine	3 mg/dL	127 µmol/L
Chloramphenicol	5 mg/dL	155 µmol/L
Chlordiazepoxide	1 mg/dL	33.3 µmol/L
Chlorpromazine	0.2 mg/dL	6.27 µmol/L
Cholesterol	500 mg/dL	12.9 mmol/L
Cimetidine	2 mg/dL	79.2 µmol/L
Creatinine	30 mg/dL	2652 µmol/L

Substance	Test Concentration	SI Units
Dextran	6000 mg/dL	1500 µmol/L
Diazepam	0.5 mg/dL	17.6 µmol/L
Digoxin	5 ng/mL	6.15 nmol/L
Erythromycin	6 mg/dL	81.6 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25 mg/dL	1770 µmol/L
Furosemide	6 mg/dL	181 µmol/L
Gentamicin	12 mg/dL	151 µmol/L
Ibuprofen	50 mg/dL	2425 µmol/L
Immunoglobulin G (IgG)	5 g/dL	50 g/L
Lidocaine	1.2 mg/dL	51.2 µmol/L
Lithium chloride	2.3 mg/dL	3.2 mmol/L
Lithium heparin	3 U/mL	3000 U/L
Nicotine	0.1 mg/dL	6.2 µmol/L
Penicillin	25 U/mL	25000 U/L
Pentobarbital	8 mg/dL	354 µmol/L
Phenobarbital	10 mg/dL	431 µmol/L
Phenytoin	5 mg/dL	198 µmol/L
Primidone	4 mg/dL	183 µmol/L
Propoxyphene	0.2 mg/dL	4.91 µmol/L
Protein, Albumin	6 g/dL	60 g/L
Rheumatoid Factors	906 IU/mL	906 IU/mL
Salicylic acid	60 mg/dL	4.34 mmol/L
Sodium heparin	3 U/mL	3000 U/L
Theophylline	4 mg/dL	95 µmol/L
Urea	500 mg/dL	83.3 mmol/L
Uric acid	20 mg/dL	1190 µmol/L
Valproic acid	50 mg/dL	3467 µmol/L

To evaluate possible interference from rheumatoid factors, 1:1 dilutions of samples with RF concentrations in the range of 978 - 1812 IU/mL and samples with no detectable RF were made and tested. The range of α2-macroglobulin in the samples used for this study was 1.52 - 4.42 g/L. Recovery of α2-macroglobulin was in the range of -2.7% to +0.7% for these samples. The acceptance criterion for the bias was ± 10%.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

De-identified serum and plasma samples containing measurable amounts of α2-macroglobulin were used in this study. The only additional requirement was a sufficient sample volume for testing. The samples were obtained from external sources. The samples were frozen within 24 hours of collection and

stored frozen (-20°C) for up to 3 months without exposure to repeated freeze-thaw cycles until tested for both the predicate and the proposed device. Sample stability studies were performed on samples stored at 2 - 8°C for seven days and frozen at -20°C for three months to validate storage conditions. There were a total of 143 samples consisting of 64 serum samples and 79 heparin (lithium and sodium) plasma samples in the method comparison study. A single determination was run for each sample following CLSI/NCCLS EP9-A2. Passing-Bablok regression analysis was used to analyze the data for the initial measuring range. The regression statistics as follows:

Serum : Slope = 1.028, Intercept = +5.7 (0.057) mg/dL (g/L)
Correlation Coefficient (r) = 0.996 , n = 64

Plasma: Slope = 1.050, Intercept = +6.0 (0.060) mg/dL (g/L)
Correlation Coefficient (r) = 0.990, n = 79

Combined: Slope = 1.042, Intercept = +6.3 (0.063) mg/dL (g/L)
Correlation Coefficient (r) = 0.993, n = 143

b. Matrix comparison:

In addition to the method comparison studies, a separate study was done using matched serum and plasma samples on the Dimension Vista® System. In this study, matched samples of serum, lithium heparin, sodium heparin and EDTA were tested on the Dimension Vista® System. The % recovery of α2-macroglobulin for each plasma type was determined versus serum and a regression analysis was done for each plasma type versus serum. The acceptance criteria were for a correlation coefficient of ≥0.950 and for a median of the normalized differences ≥ 7%. All samples met the acceptance criterion.

	Linear Regression vs. Serum			% Recovery Statistics		
	Li Hep	Na Hep	EDTA	Li Hep	Na Hep	EDTA
Slope	0.99	1.00	0.98			
Y-int	0.03	-0.03	-0.04	Mean: 0.5%	-1.4%	-4.7%
r	0.997	0.999	1.000	Min: -6.9%	-6.0%	-8.0%
Syx	0.14	0.09	0.05	Max: 8.2%	3.9%	-1.7%
Low 95% CI Slope	0.953	0.976	0.963			
High 95% CI Slope	1.03	1.03	0.99			

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:
   A literature reference was used for the expected range. The expected range interval is 130 - 300 mg/dL (1.30 - 3.0 g/L) for serum and plasma.

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.