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

A. 510(k) Number:

k071224

B. Purpose for Submission:

New device

C. Measurand:

Vitamin B12, Folate

D. Type of Test:

Quantitative

E. Applicant:

Dade Behring

F. Proprietary and Established Names:

Dimension Vista® Vitamin B12 Flex® reagent cartridge (B12)
Dimension Vista® Folate Flex® reagent cartridge (FOL)
Dimension Vista® LOCI 4 Calibrator

G. Regulatory Information:

1. Regulation section:

   21 CFR §862.1810, Vitamin B12 test system
   21 CFR §862.1295, Folic acid test system
   21 CFR §862.1150, Calibrator

2. Classification:

   Class II

3. Product code:

   CDD, CGN and JIX, respectively

4. Panel:

   75, Clinical Chemistry

H. Intended Use:

1. Intended use(s):

   See indications for use below

2. Indication(s) for use:

   Dimension Vista® Vitamin B12 Flex® reagent cartridge (B12)

   The B12 Flex® reagent cartridge is an in vitro diagnostic test for the quantitative measurement of Vitamin B12 in human serum and plasma on the Dimension Vista® system. Measurements obtained by this device are used in the diagnosis and treatment of anemias of gastrointestinal malabsorption.

   Dimension Vista® Folate Flex® reagent cartridge (FOL)

   The FOL Flex® reagent cartridge is an in vitro diagnostic test for the quantitative measurement of folate in human serum and plasma on the Dimension Vista® system. Measurements obtained by this device are used in the diagnosis and treatment of megaloblastic anemia.

   Dimension Vista® LOCI 4 Calibrator

   The LOCI 4 Calibrator is an in vitro diagnostic product for the calibration of Ferritin (FERR), Vitamin B12 (B12) and Folate (FOL) methods on the Dimension Vista® system.

3. Special conditions for use statement(s):

   For Prescription use only

4. Special instrument requirements:

   Dade Behring Dimension Vista® system

I. Device Description:

The Dimension Vista™ Vitamine B12 Flex® reagent cartridge (B12) *c*onsists of prepackaged, liquid reagents in a plastic twelve well cartridge. Each well contains the following reagent: wells 1-2 B12-Chemibeads, wells 3-4 NaOH and KCN, wells 7-8 Streptavidin Sensibeads, wells 9-10 Discyanocobinamide and wells 11-12

Biotinylated IF.

The Dimension Vista™ Folate Flex® reagent cartridge (FOL) *c*onsists of prepackaged, liquid and tablet reagents in a plastic twelve well cartridge. Each well contains the following reagent: wells 1-2 Ascorbic Acid tablet, wells 3-4 Sodium Hydroxide, wells 5-6 Dithiothreitol (DTT) tablet, wells 7-8 Folate Binding Protein and Biotinylated antibody (mouse monoclonal), wells 9-10 Folate Chemibeads and wells 11-12 Streptavidin Sensibeads.

The Dimension Vista™ LOCI 4 Calibrator is a multi-analyte liquid product containing Ferritin (cleared k070552), from human liver, Vitamin B12 and Folate in bovine serum albumin. The kit consists of ten vials, two each of five levels containing 2.5 mL per vial for level A, 1.5 mL per vial for level B, 1.0 mL per vial for levels C and D and 2.0 mL per vial for level E.

All human source material was tested by FDA-approved methods for HIV-1/2, HBsAg, and HCV and found to be negative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Elecsys Vitamin B12 Test System, Roche Diagnostics
   FOL for the Advia Centaur System, Bayer Healthcare
   FERR Calibrator for the Dimension system, Dade Behring

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

   k041133, k010050 and k983548, respectively

3. Comparison with predicate:

Similarities		
Item	Dimension Vista B12 Flex reagent cartridge	Roche Elecsys Vitamin B12 Test System
Sample Type	Serum and Plasma	Serum and Plasma
Detection	Chemiluminescent	Chemiluminescent
Binding Protein	Purified porcine Intrinsic Factor	Purified porcine Intrinsic Factor

Differences		
Item	Dimension Vista B12 Flex reagent cartridge	Roche Elecsys Vitamin B12 Test System
Assay Range	50-2000 pg/mL	30-2000 pg/mL
Technology	Competitive format	Competitive format

Differences		
Item	Dimension Vista B12 Flex reagent cartridge	Roche Elecsys Vitamin B12 Test System
	homogeneous immunoassay	heterogeneous immunoassay

Similarities		
Item	Dimension Vista FOL Flex reagent cartridge	FOL on the ADVA Centaur System
Technology	Competitive format immunoassay	Competitive format immunoassay
Detection	Chemiluminescent	Chemiluminescent

Differences		
Item	Dimension Vista FOL Flex reagent cartridge	FOL on the ADVA Centaur System
Asay Range	0.5 -20 ng/mL	0.35 – 24 ng/mL
Sample Size	10 µL	150 µL
Sample type	Serum and Plasma	Serum and Red Blood Cells

Similarities		
Item	Dimension Vista LOCI 4 Calibrator	Dimension Ferritin Calibrator
Matrix	Bovine Serum Albumin	Bovine Serum Albumin
Levels	5	5

Differences		
Item	Dimension Vista LOCI 4 Calibrator	Dimension Ferritin Calibrator
Intended Use	Calibrate Ferritin, Vitamin B12 and Folate	Calibrate Ferritin
Form	Liquid stored at 10-20 ºC	Liquid stored at 2-8 ºC

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

CLSI EP5-A2: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline
CLSI EP7-A2; Interference Testing in Clinical Chemistry; Proposed Guideline
CLSI EP6-A; Evaluation of the Linearity of Quantitative Analytical Methods
CLSI EP9-A2; Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

L. Test Principle:

The Dimension Vista Vitamin B12 and Folate Flex assays are homogeneous, competitive chemiluminescent immunoassays based on LOCI technology. The LOCI reagents include two synthetic bead reagents and binding proteins. The first bead reagent (Chemibeads) is coated with a B12 derivative for the B12 assay and folic acid derivative for the Folate assay and a chemiluminescent dye. The second bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. Samples undergo a pretreatment step. After the sample pretreatment, the binding protein and Chemibeads is added to the sample an incubated. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680nm generates singlet oxygen from the Sensibeads which diffuses to the Chemibeads and triggers a chemiluminescent reaction. The resulting chemiluminescent signal is measured at 612nm and is an inverse function of the concentration the analyte in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Repeatability testing was done in accordance with CLSI Approved Guideline for Evaluation of Precision Performance of Clinical Devices: EP5-A2. Specimens at each level were analyzed in duplicate, twice a day, for 20 days. The repeatability and within-lab standard deviations (SD) and percent coefficient of variation (%CV) were calculated by the analysis of variance method. The data are summarized below.

B12

Material	Mean pg/mL	Repeatability SD(%CV)	Within-Lab SD(%CV)
MAS Moni-Trol Level 1	219	11.2(5.1)	13.7(6.3)
MAS Moni-Trol Level 2	541	15.5(2.9)	20.1(3.7)
MAS Moni-Trol Level 3	862	10.8(1.3)	17.0(2.0)
Serum Pool 1	196	11.3(5.8)	13.9(7.1)
Serum Pool 2	1606	15.7(1.0)	24.7(1.5)
Plasma Pool 1	278	11.7(4.2)	15.6(5.6)

Folate

Material	Mean ng/mL	Repeatability SD(%CV)	Within-Lab SD(%CV)
Bio-Rad Level 1	1.9	0.11(5.8)	0.16(8.4)
Bio-Rad Level 2	4.5	0.18(3.9)	0.22(5.0)
Bio-Rad Level 3	6.0	0.26(4.4)	0.35(5.8)
Serum Pool 1	2.9	0.18(6.0)	0.21(7.2)
Serum Pool 2	17.0	0.74(4.4)	0.87(5.1)

b. Linearity/assay reportable range:

The reportable range of 50-2000 pg/mL for B12 and 0.5-20 ng/mL for Folate is based on linearity, detection limit and method comparison.
Linearity across the assay range was confirmed by testing serum samples with high concentrations of B12 and Folate. These samples were serially diluted with the zero calibrator down to the lower measuring range (2183 to 0 pg/mL B12 and 24.4 to 0 Folate) in 9 points. Each dilution was tested in replicates of five.
The linear regression was calculated.

	Slope	Intercept	Correlation Coefficient
B12	0.988	5.8	0.998
FOL	0.99	0.23	0.994

Recovery

B12
Two serum samples and one plasma sample with baseline values of B12 ranging from 217-276 were spiked with known amounts of USP B12 and samples were assayed. The percent recovery was calculated. The mean recovery was 96.5%.

Sample Type	Baseline B12 pg/mL	Spike B12 pg/mL	Expected ng/mL	Obtained ng/mL	B12 % Recovery
Serum	276	1097	13763	1283	93.4
Serum	217	1097	1314	1264	96.2
Plasma	271	1097	1368	1365	99.8

Folate
Four serum and two plasma samples containing elevated and low levels of native folate were tested individually and as a 1:1 mixture. The mean recovery was 103.6% 9.

			1:1 Mixture		
Sample Type	FOL ng/mL Low	FOL ng/mL High	Expected ng/mL	Obtained ng/mL	FOL % Recovery
Serum	1.2	17.0	9.1	8.4	92.3
Serum	4.4	18.7	11.6	13.0	112.1
Serum	3.4	17.8	10.6	11.1	104.7
Serum	2.4	17.2	9.8	10.5	107.1
Plasma	4.1	10.8	7.5	8.0	106.7
Plasma	4.4	11.5	8.0	7.9	98.8

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

Anchor pools are made by adding varying known quantities of the United States Pharmacopoeia (USP) grade B12 and Folate into a B12/Folate depleted human serum matrix. The concentrations are verified by testing patient samples with values across the range of the assay.
Standard values are assigned to a master calibrator lot using USP grade B12 and Folate into a bovine serum albumin matrix. Values are then assigned to the commercial calibrator (bovine serum albumin matrix at target concentration) verses master calibrator using instruments calibrated with the master pool. Each level is tested on mulitple instruments for a total of >40 measurements.

Un-open calibrators stored frozen at -20 to -10º C are stable until the stated expiration date. Real time calibrator stability is ongoing. Un-open thawed calibrators stored at 2 to 8º C are stable for 30 days. Open vial punctured stability was set at 3 days.

d. *Detection limit:*

The Limit of the Blank represents the lowest concentration of analyte that can be distinguished from zero and defined as the mean value (n=20 replicates) plus two standard deviations of a zero level sample. The Limit of Blank for Dimension Vista® Vitamin B12 assay and Dimension Vista® Folate assay were determined to be 20 pg/mL and 0.5 ng/mL respectively.

e. Analytical specificity:

Samples containing Vitamin B12 at a concentration of 190 pg/mL and Folate at a concentration of 2.9 ng/mL were evaluated for interference according to CLSI EP7-A. The following substances demonstrated no significant bias (defined as < 10 % difference).

Substance Tested	Substance concentration B12/Folate	Vitamin B12 pg/mL	Folate ng/mL	Bias %
Hemoglobin (hemolysate)	100 mg/dL/ Hemoglobin	190	Measurements cannot be made on hemolyzed specimens	<10
Bilirubin (unconjugated)	20 mg/dL	190	2.9	<10
Bilirubin (conjugated)	20 mg/dL	190	2.9	<10
Lipemia (Intralipid)	3000 mg/dL	190	2.9	<10

The following substances show an interference of >10%:

Substance Tested	Substance concentration	Vitamin B12 pg/mL	Bias
Albumin	6 g/dL	190	↑ results 47.1%
Dextran	40 at 6 g/dL	190	↓ results -28.2%
Immunoglobulin G	5 g/dL	190	↓ results -14.2%
Uric Acid	20 mg/dL	190	↑ results 26.2%

Substance Tested	Substance concentration	Folate ng/mL	Bias
Albumin	6 g/dL	2.9	↓ results 38%
Chlorpromazine	0.2 mg/dL	2.9	↑ results 16%
Cimetidine	2.0 mg/dL	2.9	↑ results 47%
Total Protein	12 g/dL	2.9	↓ results 42%

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

f. Assay cut-off:

Not applicable

2. Comparison studies:

   a. *Method comparison with predicate device:*

      A split sample method comparison between the Dimension Vista B12 and Roche Elecsys Vitamin B12 test system and FOL Flex reagent cartridges and the ADVIA Centaur System FOL assay were performed following CLSI EP9-A2. The correlations are as follows:

      Dimension Vista® Vitamin B12 – y = 1.037 + 16.7, r = 0.984, n = 112
      Dimension Vista® Folate – y = 0.989x + 0.02, r = 0.955, n = 110

   b. *Matrix comparison:*

      A serum and plasma comparison study was conducted to substantiate the use of sodium and lithium Heparin and EDTA anticoagulant for Vitamin B12 testing. Paired samples were analyzed by the assay on the Dimension Vista® system. The correlation was as follows:

      Na Heparin vs. Serum - y = 0.98x + 4.0, r = 0.98, n=69, range =105-1807
      Li Heparin vs. Serum - y = 0.96x + 4.7, r = 0.98, n=69, range = 111-1895
      EDTA vs. Serum - y = 0.98x + 3.1, r = 0.96, n=69, range = 134-1952

      A serum and plasma comparison study was conducted to substantiate the use of sodium and lithium heparin anticoagulant for Folate testing. Paired samples were analyzed by the assay on the Dimension Vista® system. The correlation was as follows:

      Na Heparin vs. Serum - y = 0.97x – 0.05, r = 0.97, n=40, range = 2.1-18.6
      Li Heparin vs. Serum - y = 0.97x – 0.44, r = 0.97, n=40, range = 1.8-17.3

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 Vitamin B12 reference range was determined from a population of 157 healthy adults (78 males and 79 females). The Folate reference range was obtained from the literature. Package insert states that each laboratory should establish its own expected ranges.

   Vitamin B12 – 254-1320 pg/mL (187 - 974 pmol/L)
   Folate – 3.5 – 17.5 ng/mL (7.9 – 39.6 nmol/L)

   Kratz A., Lewandrowski K. B. MGH Case Records – Normal Reference Laboratory Values. N Engl J Med. 1998; 339:15:1063-1072

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.