

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

A. 510(k) Number:

k061719

B. Purpose for Submission:

New device

New calibrator material

C. Measurand:

Bilirubin, total

D. Type of Test:

Quantitative absorbance assay

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Dimension Vista™ TBIL Flex® reagent cartridge

Dimension Vista™ TDBIL Calibrator

G. Regulatory Information:

1. Regulation section:

21 CFR § 862.1110, Bilirubin (total or direct) test system

21 CFR § 862.1150, Calibrator

2. Classification:

Class II

3. Product code:

CIG, Diazo colorimetry, bilirubin;

JIT, Calibrator

4. Panel:

Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

See below.

2. Indication(s) for use:

TBIL Flex® reagent cartridge: The TBIL method is an *in vitro* diagnostic test for the quantitative measurement of total bilirubin in human serum and plasma on the Dimension Vista™ System. Measurements of total bilirubin are used in the diagnosis and treatment of liver, hemolytic hematological and metabolic disorders, including hepatitis and gall bladder disease.

TDBIL Calibrator: The TDBIL CAL is an *in vitro* diagnostic product for calibration of the Direct Bilirubin (DBIL) and Total Bilirubin (TBIL) methods on the Dimension Vista™ System.

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

Dimension Vista™ Integrated System (k051087)

I. Device Description:

The Dimension Vista™ TBIL Flex® reagent cartridge is an *in vitro* diagnostic device that consists of prepackaged, liquid reagents in a plastic twelve well cartridge for use on the Dade Behring Dimension® clinical chemistry system for the quantitative determination of total bilirubin levels in serum and plasma. The flex cartridge contains caffeine in buffer and EDTA, a sulfanilic acid-hydrochloric acid solution, and sodium nitrite.

The Dimension Vista™ TDBIL Calibrator is packaged as three vials of a single level lyophilized product to be stored at 2-8°C. The matrix is bilirubin depleted human serum spiked with ditauobilirubin targeted to 27.5 mg/dL. Purified water, the low level calibrator, is supplied on-board the instrument. The master pool is a multi-level, lyophilized bilirubin-depleted human serum containing ditauobilirubin and is stored at -20°C.

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):

Dade Behring Dimension total bilirubin

Dade Behring Dimension TBIL/DBIL calibrator

2. Predicate K number(s):

k861700

3. Comparison with predicate:

The TBIL Flex reagent cartridge is similar to the predicate in the following ways: intended use, matrices, test principle, and reference interval. The TBIL Flex reagent cartridge is different from the predicate in the following ways:

Differences		
Item	Device	Predicate
Sample volume	5 µL	28 µL
Hemoglobin correction	Up to 1000mg/dL hemoglobin	Up to 500mg/dL hemoglobin
Analytical sensitivity	0.1 mg/dL	Not provided
Within-run precision	5% CV at 0.9 mg/dL 2.9% CV at 19.3 mg/dL	2.4% CV at 0.9 mg/dL 9.6% CV at 18.9 mg/dL

The TDBIL calibrator is similar to the predicate in the following ways: intended use, analyte, matrix, and storage form. The TDBIL calibrator is different from the predicate in the following ways:

Differences		
Item	Device	Predicate
Levels Bilirubin concentration (mg/dL) Total (TBIL) Direct (DBIL)	Three L1 (0.8), L2 (9.4), L3 (21) L1 (0.6), L2 (6.9), L3 (14.5)	One Level 2 (27.5) Level 2 (19.25) On-board purified system water is used for level 1
Volume	6 vials, 2 vials each level, 1 mL each vial (hydrated volume)	3 vials, 1mL each vial (hydrated volume)

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

STANDARDS

Title and Reference Number

Stability Testing of In Vitro Diagnostic Reagents (13640)

Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2)

Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)

Medical devices - Application of risk management to medical devices (14971:2000)

Medical Devices - Symbols to be used with medical device labels, labeling and information to be supplied (15223)

Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)

GUIDANCE			
Document Title	Office	Division	Web Page
User Fees and Refunds for Premarket Notification Submissions (510(k)s) - Guidance for Industry and FDA Staff	CDRH		http://www.fda.gov/cdrh/mdufma/guidance/1511.html
Guidance for Industry and FDA Staff - Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use			http://www.fda.gov/cdrh/ocd/guidance/4444.html
Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff			http://www.fda.gov/cdrh/oivd/guidance/1588.html

L. Test Principle:

TBIL Flex® reagent cartridge:

Diazotized sulfanilic acid is formed by combining sodium nitrite and sulfanilic acid at low pH. Bilirubin (unconjugated) in the sample is solubilized by dilution in a mixture of caffeine/benzoate/acetate/EDTA. Upon addition of the diazotized sulfanilic acid, the solubilized bilirubin including conjugated bilirubins (mono and diglucuronides) and the delta form (biliprotein-bilirubin covalently bound to albumin) is converted to diazo-bilirubin, a red chromophore representing the total bilirubin which absorbs at 540 nm and is measured using a bichromatic (540, 700 nm) endpoint technique. A sample blank correction is used.

Solubilized bilirubin + diazotized sulfanilic acid —> red chromophore (absorbs at 540 nm)

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The sponsor performed a precision evaluation study based on CLSI Document EP5-A2. During each day of testing, two separate runs, with two test samples for each test material, were analyzed for twenty days. The test material consisted of three control levels (Level 1, 2 and 3 at low, medium and high bilirubin levels within the claimed linear range of the assay) as well as a pooled serum sample. The summary of the precision results are shown below:

	Mean		Standard Deviation					
			Repeatability			Within-lab		
Material	mg/dL	[umol/L]	mg/dL	[umol/L]	(%CV)	mg/dL	[umol/L]	(%CV)
Serum pool	1.0	[17]	0.03	[0.5]	(2.7)	0.03	[0.5]	(3.3)
Lymphocheck								
Level 1	0.9	[15]	0.04	[1]	(5.0)	0.04	[1]	(5.0)
Level 2	4.4	[75]	0.10	[2]	(2.4)	0.11	[2]	(2.6)
MAS Bilirubin								
Level 3	19.3	[330]	0.31	[5]	(1.6)	0.56	[10]	(2.9)

b. *Linearity/assay reportable range:*

The reportable range this assay is 0.1-25.0 mg/dL [2 - 428 µmol/L].

Linearity was evaluated by comparing the observed versus expected values obtained with the Dimension Vista TBIL method using eleven samples at various concentrations. Data generated during this study indicate an acceptable assay recovery from 0.1 to 25.0 mg/dL with percent recoveries within 10% of the predicted values.

Regression Statistics (linear least square)

Slope: 0.98

Y-intercept: -0.24

r: 1.000

The sponsor recommends that samples with results in excess of 25.0 mg/dL [428µmol/L] be repeated after dilution. Accurate dilution of samples using the recommended diluent (CLSI type 1 Reagent grade water) was demonstrated by diluting multiple elevated samples at a 1:4 ratio. The results support the sponsor's recommendation for diluted samples.

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

Stability: Shelf life for this calibrator is 12 months. Open vial testing protocols and acceptance criteria were described and found to be acceptable.

Traceability and Value Assignment: Values are assigned to the master pool by calibrating the Dimension® Total Bilirubin method with freshly prepared

National Institute of Technology (NIST) Standard Reference Material (SRM) 916, Bilirubin at five levels across the assay range.

Since there is no reference standard for direct bilirubin, the DBIL values are assigned based on the ratio of direct and total bilirubin as determined by Doumas et. al., Clin Chem 1985;31:1677-1682, and the method differences versus the Jendrassik Grof assay. DBIL value is calculated as 70% of the total bilirubin assignment.

d. Detection limit:

Twenty consecutive measurements of a sample devoid of bilirubin were tested on the Dimension Vista™ system. Analytical sensitivity was defined as the concentration at two standard deviations above the mean of the twenty replicates. The analytical sensitivity of the Dimension Vista™ TBIL method tested with water is 0.05 mg/dL. The sponsor is using a slightly wider product claim of 0.1 mg/dL on the product labeling to accommodate instrument-to-instrument variability.

e. Analytical specificity:

The Dimension Vista™ TBIL assay was evaluated for interference using a protocol developed according to CLSI Document EP7-A2 8. Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in mg/dL [μmol/L]. Bias exceeding 10% was considered interference.

Substance tested	Substance concentration	Total bilirubin mg/dL [μmol/L]	Bias %
Levodopa	300 μg/mL [1.52 mmol/L]	1.2 [21]	108%
Phenazopyridine	80 μg/mL [320 μmol/L]	1.2 [21]	50%
Triglycerides	3000 mg/dL [33.9 mmol/L]	0.9 [15]	-11%
Salicylic acid	60 mg/dL [4.34 mmol/L]	25[428]	-11%

Other exogenous substances found to not interfere with the TBIL method are listed in the package insert. Inaccuracies (biases) due to these substances are less than 10% at total bilirubin concentrations of 1.0 - 1.2 mg/dL and 21.0 - 27.1 mg/dL.

The potential for interference from endogenous substances (lipids and hemoglobin) was evaluated. Results are summarized below:

Substance Tested	Substance Concentration	TBIL mg/dL [μmol/L]	Bias* %
Hemoglobin	Hemoglobin (monomer)	1.1 [19]	<10%
(hemolysate)	1000 mg/dL [0.62 mmol/L]	25 [428]	<10%

Lipemia)	800 mg/dL [9.0 mmol/L]	1.1 [19]	10%
(Intralipid®)	1000 mg/dL [11.3 mmol/L]	1.2 [20]	20%
	3000 mg/dL [33.9 mmol/L]	1.4 [24]	40%
	3000 mg/dL [33.9 mmol/L]	21 [359]	<10%

*The package insert states that Analyte results should not be corrected based on this bias.

f. *Assay cut-off:*
Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

A split sample method comparison was conducted with one hundred fifty serum samples using the Dimension TBIL (predicate) and Dimension Vista™ TBIL assays. The samples were analyzed in duplicate on the Dimension and Dimension Vista™ systems. The model equation for the linear least squares regression statistics is: [results for Dimension Vista™ System] = slope x [comparative method results] + intercept. A regression slope of 0.942, intercept of 0.039 mg/dL and correlation of 0.999 demonstrate acceptable agreement between the assays. The range of TBIL values in the correlation study was: 0.11 to 23.4 mg/dL.

b. *Matrix comparison:*

A split sample method comparison was conducted on two different days with a total of sixty-four matched serum, EDTA plasma and lithium heparin plasma samples using the Dimension Vista™ TBIL assay. The samples were analyzed in duplicate. The model equation for the linear least squares regression statistics is: [results for Dimension Vista™ System] = slope x [comparative method results] + intercept. The regression of the mean results provided slopes that ranged from 0.98 to 1.01, intercepts from -0.15 to 0.32 mg/dL and correlation of 0.993 to 0.994.

Sample comparison	Slope	Intercept		Correlation Coefficient	N
		mg/dL	[μmol/L]		
Lithium heparin plasma vs. serum	0.978	0.3	[5]	0.993	61 ^a
EDTA plasma vs. serum	0.972	0.3	[5]	0.993	61 ^b
EDTA plasma vs. lithium heparin plasma	1.008	-0.2	[-3]	0.993	61 ^c

a. The range of TBIL values in the correlation study was 0.2-24.2 mg/dL [3-414 μmol/L]

b. The range of TBIL values in the correlation study was 0.1-24.4 mg/dL [2-417 μmol/L]

c. The range of TBIL values in the correlation study was 0.1-24.4 mg/dL [2-417 μmol/L]

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:

Expected Values: 0.2-1.0 mg/dL [3-17 µmol/L] as referenced from Tietz, NW, Textbook of Clinical Chemistry, W.B. Saunders Co., Philadelphia, PA 1986, p 1815. In addition, the sponsor obtained serum samples from thirty-one apparently healthy donors and examined them to verify the reference interval stated in the literature (Kaplan, LA, Pesce, AJ. Clinical Chemistry: Theory, Analysis, and Correlation, 3rd ed. St. Louis, MO: Mosby, Inc, 1996: p. 712). The values obtained ranged from 0.3 to 1.1 mg/dL.

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.