

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

A. 510(k) Number:

k061839

B. Purpose for Submission:

510(k) premarket notification to manufacture and market the Dimension Vista™ DBIL Flex® reagent cartridge

C. Measurand:

Direct Bilirubin

D. Type of Test:

Diazo Colorimetry

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Dimension Vista™ DBIL Flex® reagent cartridge

G. Regulatory Information:

1. Regulation section:

862.1110 – Bilirubin (total or direct) test system.

2. Classification:

Class II

3. Product code:

CIG - Diazo colorimetry, bilirubin

4. Panel:

Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indication(s) for use below.

2. Indication(s) for use:

The DBIL method is an in vitro diagnostic test for the quantitative measurement of direct (conjugated) bilirubin in human serum and plasma on the Dimension Vista™ System. Measurements of direct bilirubin are used in the diagnosis and treatment of liver, hemolytic, hematological and metabolic disorders, including hepatitis and gall bladder disease.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

Dimension Vista™ System

I. Device Description:

Diazotized sulfanilic acid is formed by combining sodium nitrite and sulfanilic acid at low pH. The sample is diluted in 0.5M HCl. A blank reading is taken to eliminate interference from nonbilirubin pigments. Upon addition of the diazotized sulfanilic acid, the conjugated bilirubin is converted to diazo-bilirubin, a red chromophore which absorbs at 540 nm and is measured using a bichromatic (540, 700 nm) endpoint technique.

Conjugated bilirubin + Diazotized sulfanilic acid ———> Red chromophore (absorbs at 540 nm)

J. Substantial Equivalence Information:

1. Predicate device name(s):

Dade Behring DBIL Flex® reagent cartridge

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

k862359

3. Comparison with predicate:

Similarities		
Item	Dimension Vista™ DBIL (Device)	Dimension® DBIL Assay (Predicate k862359)
Sample type	Human serum and plasma	Human serum and plasma
Methodology	Photometric (diazo chemistry)	Photometric (diazo chemistry)
Detection	Bichromatic (540, 700 nm)	Bichromatic (540, 700 nm)
Hemoglobin Flag	Yes	Yes
Differences		
Item	Dimension Vista™ DBIL (Device)	Dimension® DBIL Assay (Predicate k862359)
Intended Use	The DBIL method is an <i>in vitro</i> diagnostic test for the quantitative measurement of direct (conjugated) bilirubin in human serum and plasma on the Dimension Vista™ System. Measurements of direct bilirubin are used in the diagnosis and treatment of liver, hemolytic, hematological and metabolic disorders, including hepatitis and gall bladder disease.	The DBIL method used on the Dimension® clinical chemistry system is an <i>in vitro</i> diagnostic test intended for the quantitative determination of direct (conjugated) bilirubin in serum and plasma.
Sample volume	5 µL	31 µL
Analytical Sensitivity	0.05 mg/dL	Not provided
Repeatability	9.1% CV @ 0.4 mg/dL 2.1% CV @ 5.9 mg/dL	4.7 % CV at 5 mg/dL
Reference Interval	< 0.2 mg/dL	< 0.3 mg/dL

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

FDA Guidance for Industry and FDA Staff - Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use

FDA Guidance for Industry and FDA Staff - User Fees and Refunds for Premarket Notification Submissions (510(k)s)

FDA Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff - Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable

CEN 13640, Stability Testing of In Vitro Diagnostic Reagents

CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

CLSI EP7-A, Interference Testing in Clinical Chemistry; Approved Guideline

ISO 14971:2000, Medical devices - Application of risk management to medical devices

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

CLSI EP5-A, Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline

L. Test Principle:

The assay employs a modified diazo method whereby the addition of diazotized sulfanilic acid to conjugated bilirubin causes a conversion to diazo-bilirubin, which absorbs at 540 nm. Measurement is performed by a bichromatic endpoint technique.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A twenty day ANOVA study was conducted per CLSI EP5A2. Quality control materials and serum pools were examined at various concentrations across the assay range. QC materials and serum pools were examined near 0.4 mg/dL, an important medical decision level. See attached results.

Material	mg/dL	Mean	Standard Deviation (%CV)					
		[$\mu\text{mol/L}$]	Repeatability			Within-Lab		
Serum Pool 1	0.4	[7]	0.02	[0.3]	(5.7)	0.02	[0.3]	(5.7)
Serum Pool 2	13.8	[237]	0.22	[4]	(1.6)	0.37	[6]	(2.7)
Lyphochek®								
Level 1	0.4	[7]	0.03	[0.5]	(8.9)	0.03	[0.5]	(9.1)
Level 2	1.6	[27]	0.03	[0.5]	(2.1)	0.04	[1]	(2.3)
MAS® Bilirubin Level 3	5.9	[101]	0.06	[1]	(1.1)	0.12	[2]	(2.1)

b. *Linearity/assay reportable range:*

The reportable range of the assay is claimed as 0.05 – 16.0 mg/dL.

Various mixtures (ratios) of the level 2 TDBIL calibrator (lyophilized human serum based product containing bilirubin), and a low concentration total bilirubin serum sample were tested. The test results were examined versus the expected value using linear least squares analysis. See the table below for the test data, acceptance criteria and data analysis.

Expected	Observed	Expected - Observed	Acceptance Criteria (Difference not to exceed ± 10% of Exp. Value)
mg/dL	mg/dL	mg/dL	mg/dL
0.2	0.2	0.0	0.02
2.6	3.0	-0.3	0.26
3.9	4.4	-0.5	0.39
5.1	5.8	-0.7	0.51
7.6	8.3	-0.7	0.76
10.1	11.0	-0.9	1.01
12.5	13.6	-1.0	1.25
15.0	16.0	-1.0	1.50
16.3	17.1	-0.9	1.63
17.5	18.1	-0.6	1.75
20.0	20.0	0.0	2.00

Regression Statistics (linear least square)	
Slope:	1.01
Y-int:	0.48
r:	0.999
r ² :	0.997

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

Not Applicable

d. *Detection limit:*

Twenty consecutive measurements of a sample devoid of bilirubin were tested on the Dimension Vista™ system with the DBIL assay. Analytical sensitivity is defined as the concentration at two standard deviations above the mean. The analytical sensitivity of the DBIL method tested with water is 0.05 mg/dL.

e. *Analytical specificity:*

Testing for interfering substances was performed as described in CLSI EP-7A. Effects of interfering substances, including endogenous substances and

commonly ingested substances were tested by spiking a serum sample at a desired direct bilirubin concentration with the appropriate concentration of the test substance. The direct bilirubin recovery of the sample was compared to that of a control sample.

Two base pools of human sera were prepared at direct bilirubin concentrations of approximately 0.3 mg/dL and 5 mg/dL. Stock solutions of each potential interfering substance of interest were prepared using the appropriate diluents.

Test samples were prepared by spiking the base pool with the respective (interferent) stock solutions. Appropriate controls were prepared by spiking base pool with diluent used to make the stock solution(s). Interference is calculated as the difference between the mean of the test and the control sample analyte response.

If the difference in recovery between the test sample and control was less than 10% it was concluded that the substance did not interfere in the method. If recovery was greater than 10%, the information was included in the Limitations section of the product insert sheet.

Substance	Substance Concentration [SI Units]	Direct Bilirubin mg/dL [µmol/L]	Bias* %
Immunoglobulin G (IgG)	5 g/dL [50 g/L]	0.4 [7]	-29%
Triglycerides	3000 mg/dL [33.9 mol/L]	0.3 [5]	-22%
Hemoglobin ⁱ (Hemolysate)	10 mg/dL[0.01 mmol/L]	0.4 [7]	-25.0%
	10 mg/dL[0.01 mmol/L]	4.0 [68]	-2.4%
	10 mg/dL[0.01 mmol/L]	15.8 [270]	-2.5%
	25 mg/dL [0.02 mmol/L]	0.4 [7]	-33%
	25 mg/dL [0.02 mmol/L]	4.2 [72]	-16.7%
	25 mg/dL [0.02 mmol/L]	15.9 [272]	-8.2%
	50 mg/dL [0.03 mmol/L]	0.3[6]	-66.7%
	50 mg/dL [0.03 mmol/L]	4.2[72]	-20.9%
	50 mg/dL [0.03 mmol/L]	15.6[267]	-8.3%
	1000 mg/dL [11.30 mmol/L]	0.4 [7]	<10%
Lipemia (Intralipid®)	3000 mg/dL [33.90 mmol/L]	0.4 [7]	50%
	3000 mg/dL [33.90 mmol/L]	5.1 [87]	<10%
	3000 mg/dL [33.90 mmol/L]	14.1 [241]	<10%

*Analyte results should not be corrected based on this bias.

ⁱ Hemolyzed samples containing 50 mg/dL [0.03 mmol/L] or greater of hemoglobin will be flagged with a “Hemoglobin” error message.

Common drugs and other exogenous and endogenous substances that do not interfere with the assay are listed in the Non Interfering Substances section of the instructions for use.

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 patient samples (118 serum and 32 plasma) using the Dimension® DBIL (predicate) and Dimension Vista™ assays. The samples were analyzed randomly in duplicate on the two systems. The model equation for the linear least squares regression statistics is: [results for Dimension Vista(TM) system] = slope x [comparative method results] + intercept. Twenty-eight samples were outside the assay range of one of the analyzers and excluded from the statistical analysis. A regression slope of 0.971, intercept of 0.01 mg/dL and correlation coefficient of 0.999 demonstrate good agreement between the assays. The range of DBIL values in the correlation study was 0.04 to 15.75 mg/dL.

b. *Matrix comparison:*

A split sample 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™ DBIL assay. Different DBIL reagents and instruments were used on each day of the study. The samples were analyzed in duplicate. The data was examined using linear least squares analysis. Seven to nine samples were outside the assay range (depending on the sample type) and excluded from the statistical analysis. The regression of the mean results provided slopes that ranged from 0.96 to 1.05, intercepts from -0.33 to 0.06 mg/dL and correlation coefficients of 0.994 to 0.998. The data demonstrate excellent agreement between the sample types. The range of DBIL values in the correlation study was 0.1 to 16 mg/dL.

Serum vs. Lithium Heparin		Serum vs. EDTA		EDTA vs. Lithium Heparin	
Slope:	1.012	Slope:	0.961	Slope:	1.049
Intercept:	-0.308	Intercept:	-0.326	Intercept:	0.059
r:	0.994	r:	0.998	r:	0.994
r2:	0.989	r2:	0.995	r2:	0.988
n:	55	n:	55	n:	57

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 – 0.2 mg/dL [0 –3 µmol/L]

(Kaplan LA, Pesce AJ. Clinical Chemistry: Theory, Analysis, and Correlation, 3rd ed. St. Louis, MO: Mosby, Inc, 1996: p. 712.)

The reference interval was verified using 31 serum samples.

The package insert recommends that each laboratory should establish its own expected values for DBIL as performed on the Dimension Vista™ System.

The assay performance has not been established/tested for neonate population.

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.