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

A. 510(k) Number:
k082210

B. Purpose for Submission:
New 510(k)

C. Measurand:
Total Bilirubin

D. Type of Test:
Quantitative, Photometric

E. Applicant:
Genzyme Diagnostics P.E.I. Inc.

F. Proprietary and Established Names:
Total Bilirubin L3K, Model 295-10 and 295-30

G. Regulatory Information:
1. Regulation section:
   21CFR Sec.- 862.1110-Bilirubin (total or direct) test system.

2. Classification:
   Class 2

3. Product code:
   CIG - Diazo Colorimetry, Bilirubin

4. Panel:
   Chemistry (75)

H. Intended Use:
1. Intended use(s):
   See indication(s) for use below.

2. Indication(s) for use:
   For the IN VITRO quantitative measurement of Total Bilirubin in serum and plasma

   Measurement of Total Bilirubin is used in the diagnosis and management of liver disease, biliary tract obstruction, various hemolytic diseases and disorders involving the metabolism of bilirubin.

3. Special conditions for use statement(s):
   For prescription use

4. Special instrument requirements:
   Hitachi 911 Analyzer

I. Device Description:

Reagent is a two-part liquid in plastic bottles packaged in the appropriate sized box.

Total Bilirubin L3K Accelerator Reagent (R1): a solution containing buffer (pH of 1.1 at 25°C), 154 mmol/L NaCl, 190 mmol/L HCl, surfactants, and preservatives.

Total Bilirubin L3K Diazo Reagent (R2): a solution containing buffer (pH of 0.9 at 25°C), 417 mmol/L HCl, 5 mmol/L 2,4 dichlorophenyldiazonium salt and surfactant.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Roche Diagnostics Corporation Total Bilirubin Reagent

2. Predicate 510(k) number(s):
   k910591

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	same	same
Reagent Format	ready to use liquid format	ready to use liquid format
Test principle	diazonium ion test principle	diazonium ion test principle

Differences		
Item	Device	Predicate
Active ingredients	Concentrations of active ingredients differ between the predicate and submission devices.	

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

- Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)
- Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2)

- Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)
- Medical devices - Application of risk management to medical devices (14971:2000)

L. Test Principle:
Total Bilirubin L3K Assay couples the bilirubin (conjugated and unconjugated) with the diazo reagent in the presence of a surfactant to form azobilirubin. The increase of absorbance at 546 nm is directly proportional to the total bilirubin concentration.

M. Performance Characteristics (if/when applicable):
1. <u>Analytical performance:</u>
   a. *Precision/Reproducibility:*
      Total precision was conducted with 40 runs performed on 20 different days using the Hitachi 911 analyzer. Each run consisted on 2 concentrations of serum controls each run in duplicate. They were run on the same instrument twice a day by one operator in Genzyme Diagnostics, P.E.I., Inc laboratories.

      Simple precision study was conducted on two concentrations of serum controls each run 10 times in 4 instrument runs over four days. The results are presented below for both studies.

Concentration		Total SD		Total CV%	Concentration		Simple SD		Simple CV %
mg/dL	µmol/L	mg/dL	µmol/L		mg/dL	µmol/L	mg/dL	µmol/L	
0.9	15.4	0.05	0.9	5.4	0.9	15.4	0.02	0.3	2.5
4.6	78.7	0.21	3.6	4.6	4.5	77.0	0.11	1.9	2.5

      In another study, total precision data was collected on a high third concentration of control sera in 40 runs over 10 days using the Hitachi 911 analyzer. Within-run precision data was collected by assaying twenty samples of one concentration of control sera in one run. The results are presented below.

Concentration		Total SD		Total CV%	Concentration		Simple SD		Simple CV%
mg/dL	µmol/L	mg/dL	µmol/L		mg/dL	µmol/L	mg/dL	µmol/L	
16.0	273.6	0.42	7.2	2.6	15.9	271.9	0.15	2.6	1.0

   b. *Linearity/assay reportable range:*

      Linearity was evaluated using samples from 0.1 mg/dL to 43.9 mg/dL on the Hitachi 911. The reportable range claim is 0.1 - 35.0 mg/dL. . The maximum deviation for a mean recovery from 100% was 3.1 %. The regression

equation for the linearity study was y = 0.988 x + 0.001.

Sample	Observed Value	Target Value	% Recovery
1	0.037	0.000	±0.1 mg/dL
2	4.365	4.37	99.9 %
3	8.707	8.73	99.7%
4	12.795	13.10	97.7%
5	17.210	17.46	98.6%
6	21.610	21.83	99.0%
7	25.390	26.19	96.9%
8	30.788	30.56	100.7%
9	34.758	34.92	99.5%
10	38.605	39.29	98.3%
11	43.852	43.65	100.5%

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
No traceability for the assay was provided. The control and calibrator materials were previously cleared in the following 510(k)s:
DC-LIQUICAL - k882258
DC-TROL LEVEL 1 OR 2 - k874772

d. *Detection limit:*
LoB = mean of blank samples (0.012) + 1.645SD. (SD of blank samples (0.014))

The limit of blank is established as the absolute mean concentration value of blank samples plus (1.645 multiplied by the standard deviation of the blank samples).

LoD = LoB + 1.645SD. (SD of low limit samples)

The limit of detection is established as the limit of blank plus (1.645 multiplied by the standard deviation of the low limit samples (0.016).

The lowest concentration sample with estimated Total Error < target Total Error (20%), and a concentration greater than the LoD (0.06 mg/dL) was the 0.1 mg/dL sample, indicating a LoQ of 0.1 mg/dL on the Hitachi 911.

Limit of blank is equal to 0.035 mg/dL
Limit of Detection is equal to 0.06 mg/dL

Limit of Quantitation is equal to 0.1 mg/dL

e. *Analytical specificity:*

Interferences from hemolysis, lipemia, and ascorbic acid were evaluated for this total bilirubin method on a Hitachi 911 analyzer using a significance criteria of >10% from control. Two concentrations of total bilirubin were evaluated. Interference data was collected in serum. Plasma data is expected to be similar.

Concentration of Total Bilirubin		Substance Tested	Concentration of Substance Where No Significant Interference was Observed	
mg/dL	µmol/L		mg/dL	µmol/L
1.4	23.9	Hemoglobin	1000	155
14.3	244.7		1000	155
mg/dL	µmol/L	Ascorbic Acid	µg/dL	mmol/L
1.4	24.1		3000	170
13.3	226.9		3000	170
mg/dL	µmol/L	Intralipid	mg/dL	(mmol/L)
1.6	28.0		1000	33.9
16.5	281.8		1000	33.9)

Testing was also done using serum collected in Lithium Heparin tubes and Sodium Heparin tubes. Serum was pooled and allocated between a control tube and either a Lithium heparin tube or a Sodium Heparin tube (test). Each test sample was inverted in the tube several times. The control pool and test pools have the same concentration of the analyte being tested, but the control pool was not been exposed to the anticoagulant being tested. Intermediate concentrations of anticoagulant was be prepared by making mixtures of the test and control pools.

No interference was found in Sodium Heparin and Lithium Heparin anticoagulant samples at concentrations up to 5 times the normal exposure to the anticoagulant.

Interference assessed by dose response. The interference was defined using a significance criterion ±10% variance from control.

f. *Assay cut-off:*
Not Applicable

2. Comparison studies:
   a. *Method comparison with predicate device:*

   A comparison was made between this method and a similar method using 98 samples including neonates in serum ranging from 0.2 mg/dL to 32.0 mg/dL on the Hitachi 911. The correlation coefficient was 0.9982. Linear regression

analysis gave the following equation:

This method = 1.05(reference method) + 0.3 mg/dL.

Neonatal samples in the range of 0.16 to 9.41 mg/dL were separately analyzed to the reference method yielding a correlation coefficient of 0.9992 and the following regression equation:

This method = 1.08 (reference method) + 0.271

    b. *Matrix comparison:*
The samples used in the matrix study were serum and plasma samples collected in Lithium Heparin and Sodium Heparin tubes in a hospital environment.

Plasma, Lithium Heparin vs. serum

A comparison was made between plasma (Lithium Heparin) and serum using 49 patient samples ranging from 0.1-34.32 mg/dL Hitachi 911. The correlation coefficient was 0.9942. Deming regression analysis gave the following equation:

Plasma = 1.06(serum) - 0.2 mg/dL.   n = 49

Plasma, Na Heparin vs. serum

A comparison was made between plasma and serum using 39 patient samples ranging from 0.2-31.49 mg/dL Hitachi 911. The correlation coefficient was 0.9851. Deming regression analysis gave the following equation:

Plasma = 0.99(serum) - 0.02 mg/dL.   n = 39

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:

    0.2-1.0 mg/dL (3.4-17.1 μmol/L)

Neonates:	Premature	Full-Term
0-1 days	<8 mg/dL (<136.8 μmol/L)	2-6 mg/dL (34.2-102.6 μmol/L)
1-2 days	<12 mg/dL (<205.2 μmol/L)	6-10 mg/dL (102.6-171.0 μmol/L)
3-5 days	<14 mg/dL (<239.4 μmol/L)	4-8 mg/dL (68.4-136.8 μmol/L)(6)

    Burtis, C.A. and Ashwood, E.R. (Eds) Tietz Textbook of Clinical Chemistry, Second Edition, W.B. Sanders Co., Philadelphia (1994).

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.