DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

RANDOX LABORATORIES LIMITED
PAULINE ARMSTRONG, QA/RA MANAGER
55 DIAMOND ROAD, ARDMORE
CRUMLIN, COUNTY ANTRIM BT29 4QY,
GREAT BRITAIN

January 28, 2016

Re: K152344
Trade/Device Name: Total Bilirubin (T BIL)
Regulation Number: 21 CFR 862.1110
Regulation Name: Bilirubin (total or direct) test system
Regulatory Class: II
Product Code: JFM
Dated: December 15, 2015
Received: December 17, 2015

Dear Pauline Armstrong:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k152344

Device Name
Total Bilirubin (TBIL)

Indications for Use *(Describe)*
For the quantitative in vitro determination of Total Bilirubin for serum and plasma. Total Bilirubin measurements are used in the diagnosis and treatment of hemolytic, biliary and liver disorders, including hepatitis and cirrhosis.

This in vitro diagnostic device is intended for prescription use only.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(K) SUMMARY, TOTAL BILIRUBIN ASSAY

1. SAFETY AND EFFECTIVENESS AS REQUIRED BY 21 CFR 807.92 STATEMENT

This summary of the 510(k) safety and effectiveness information is being submitted in accordance with the requirement 21 CFR 807.92.

2. SUBMITTER NAME AND ADDRESS

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Date of Summary Preparation: December 7, 2015

3. 510k NUMBER, DEVICE PROPRIETARY NAME, COMMON NAME, PURPOSE FOR SUBMISSION, REGULATORY CLASSIFCATION, PANEL, PRODUCT CODE AND 21 CFR NUMBER

510k No: K152344

Device Proprietary Name: Total Bilirubin (T BIL)

Common Name: Total Bilirubin

Purpose for Submission: New Device

Product Code	Regulation Name	Classification	Regulation Section	Panel
JFM	Bilirubin (Total or Direct) Test System	Class II	21 CFR 862.1110	Clinical Chemistry (75)

4. PREDICATE DEVICE PROPRIETARY NAMES AND 510 (k) NUMBERS

Predicate Device Proprietary Name:
Siemens Healthcare Diagnostic Inc (formerly Bayer Healthcare), Total Bilirubin_2 reagent

510 (k) Number: K063845

5. INTENDED USE

For the quantitative in vitro determination of Total Bilirubin in serum and plasma. Total Bilirubin measurements are used in the diagnosis and treatment of hemolytic, biliary and liver disorders, including hepatitis and cirrhosis.

This in vitro diagnostic device is intended for prescription use only.

6. DEVICE DESCRIPTION

The Total Bilirubin kit assay consists of ready to use reagent solutions.

CATALOGUE NUMBER: BR8307

R1. Total Bilirubin R1 4 x 20 mL
R2. Total Bilirubin R2 4 x 8 mL

REAGENT COMPOSITION

Contents	Initial Concentration of Solutions
R1. Total Bilirubin R1	
Citrate buffer, pH2.9	0.1 mol/L
Detergent	0.9%
Antimicrobial	
R2. Total Bilirubin R2	
Phosphate buffer, pH 7.0	10 mmol/L
Sodium Metavanadate	4 mmol/L

MATERIALS REQUIRED BUT NOT PROVIDED

Randox Assayed Multisera Level 2 (Cat. No. HN 1530) and
Level 3 (Cat. No. HE 1532); 510(k) # k942458
Randox Calibration Serum Level 3 (Cat. No. CAL 2351); 510(k) # k053153
RX series Saline (Cat. No. SA 8396)

7. PREDICATE DEVICE COMPARISON TABLE

Table 1 **Comparison of Total Bilirubin test system for the RX Daytona plus to predicate device**

CHARACTERISTICS	Total Bilirubin Assay for RX daytona plus *(New Device)*	*Siemens Healthcare Diagnostic Inc, Total Bilirubin_2 reagent (K063845) (Predicate Device)*
Similarities		
INTENDED USE	For the quantitative in vitro determination of Total Bilirubin in serum and plasma. Total Bilirubin measurements are used in the diagnosis and treatment of hemolytic, biliary and liver disorders, including hepatitis and cirrhosis.	Same
ASSAY PROTOCOL	Vanadate Oxidation Method	Same
CONTROL FREQUENCY	Randox assayed human multisera Level 2 & 3 Two levels of control should be assayed at least once a day	Same
SAMPLE TYPE	Serum, heparinized plasma samples are suitable.	Same
REAGENT COMPOSITION	Contents — Initial Concentration of Solutions **R1.** **Total Bilirubin R1** Citrate buffer, pH2.9 — 0.1 mol/L Detergent — 0.9% Antimicrobial **R2.** **Total Bilirubin R2** Phosphate buffer, pH 7.0 — 10 mmol/L Sodium Metavanadate — 4 mmol/L	Same

	Differences	
TEST RANGE	0.21 – 26.3 mg/dL	0.1 – 35 mg/dL
STORAGE (UNOPENED)	Reagents are stable up to the expiry date when stored unopened at +2 to +8°C	Reagents are stable up to the expiry date when stored unopened at +2 to +35°C
CALIBRATION FREQUENCY	Every 28 days, with a change of reagent lot or as indicated by quality control procedures.	Every 60 days.

8. TEST PRINCIPLE [(1)]

The bilirubin is oxidised by vanadate at about pH 2.9 to produce biliverdin. In the presence of detergent and vanadate, both conjugate (direct) and unconjugated bilirubin are oxidised. This oxidation reaction causes a decrease in the optical density of the yellow colour, which is specific to bilirubin. The decrease in optical density at 450/546 nm is proportional to the total bilirubin concentration in the sample. The concentration is measured as an endpoint reaction.

Bilirubin + Surfactant + VO3- ⟶ Biliverdin

1. Tokuda K, Tanimoto K. New method of measuring serum bilirubin using vanadic acid. Jpn J Clin Chem. 1993:22:116-122.2.

9. PERFORMANCE CHARACTERISTICS

Analytical performance:

a. Precision/Reproducibility:
Precision was evaluated consistent with C.L.S.I documents EP5-A2
Precision studies were performed by two operators on two RX Daytona plus systems using serum based control material and unaltered human serum samples that were spiked with unconjugated Bilirubin or diluted to achieve Total Bilirubin concentrations based on normal ranges 0.3 – 1.2 mg/dL. Testing was conducted for two reagent lots of Total Bilirubin, one lot on each RX Daytona plus system, twice per day for 20 non-consecutive days. Two replicates per run were performed for each sample. The assay was calibrated initially with no further calibration required. The results are summarized in the following tables.

Table 2 **Precision Summary**

Lot 2			MEAN	Within Run		Among Run		Among Day		Total	
Method	**Product**	**N**	**(mg/dl)**	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**
TBIL	LIN Pool	80	25.0	0.23	0.9	0.14	0.6	0.32	1.3	0.41	1.7
TBIL	LOQ Pool	80	0.3	0.02	6.9	0.01	2.6	0.00	0.0	0.02	7.4
TBIL	QC 1	80	1.5	0.04	2.9	0.02	1.6	0.01	0.7	0.05	3.4
TBIL	QC 2	80	5.3	0.08	1.5	0.03	0.5	0.13	2.5	0.16	3.0
TBIL	Serum Pool 1	80	1.1	0.05	4.0	0.03	2.4	0.03	2.8	0.06	5.4
TBIL	Serum Pool 2	80	6.7	0.11	1.6	0.08	1.1	0.09	1.4	0.16	2.4
TBIL	Serum Pool 3	80	12.0	0.12	1.0	0.07	0.6	0.24	2.0	0.28	2.3
TBIL	Serum Pool 4	80	16.2	0.15	0.9	0.21	1.3	0.24	1.5	0.35	2.2

b. Linearity/assay reportable range:

Linearity studies have been carried out in accordance with C.L.S.I. standard EP6-A. Linearity studies were performed at 11 levels to determine the analytical range of an assay - that is the range where the reported result is a linear function to the analyte concentration (or where deviation from linearity is less than 5%).

The linearity samples were prepared at 11 levels. The sponsor set a range from 0.21 mg/dl analyte concentration up to a high concentration approximately 26.3 mg/dl using low and high serum pools. The low and high pools were mixed to make nine intermediate levels. Each level was run in replicates of five on two lots of Total Bilirubin reagent on one RX Daytona plus system. The observed values were compared to the expected values; the linear regression correlation between the expected values and the observed values are summarized in the following table:

Table 3 **Linearity Summary including Regression equation and correlation co-efficient.**

Analyte Tested	Total Bilirubin (mg/dL)
Linear Regression	Y = 1.02 + 0.01
r	0.9999

Analyte	**Linearity**	**Reportable Range**
TBIL	26.3 mg/dl	0.21 – 26.3 mg/dl

The low end of the reportable assay range is based on the Limit of Quantitation.
The high end of the reportable assay range is based on the linearity.
The Rx Daytona Plus analyzer has an auto-dilution feature that is automatically activated when measuring samples >26.3 mg/dL, which are diluted and re-measured to obtain values within the measuring range.

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

Refer to K942458 Randox Assayed Multisera Level 2 and Level 3.

Refer to K053153 Randox Calibration Serum Level 3.

Randox Calibration Serum Level 3 for Total Bilirubin is traceable to an internal master reference material.

d. Detection limit:

Sensitivity studies have been carried out in accordance with C.L.S.I. guideline EP17-A2 'Evaluation of detection capability for clinical laboratory measurement procedures; Approved Guideline Second Edition'. A Limit of Blank (L.o.B.), a Limit of Detection (L.o.D.) and a Limit of Quantification were performed on two lots of reagents tested by two operators on one RX Daytona Plus system.

The Limit of Detection (LoD) for Total Bilirubin on the RX Daytona Plus is 0.08 mg/dL based on 240 determinations, with 4 low level samples.

The Limit of Blank (LoB) is 0.06 mg/dL.

The Limit of Quantitation (LoQ) is 0.21 mg/dL as determined by the lowest concentration at which precision is still met.

e. Analytical Specificity:

Interference studies have been carried out in accordance with C.L.S.I. guideline EP7-A2 'Interference testing in clinical chemistry; Approved Guideline Second Edition' The effects of potential interferents were determined by calculating the mean value of the spiked interferent with the corresponding control solution. The spiked sample results were compared to control samples prepared without the potential interferents.

Acceptance Criteria:
The criteria for no significant interference is recovery within ±10% of the initial value of Total Bilirubin concentration of 0.99 mg/dL and 15.03 mg/dL

Haemoglobin	No significant interference up to 1000mg/dL
Triglycerides	No significant interference up to 2000mg/dL
Intralipid®	No significant interference up to 1000mg/dL
Ascorbic Acid	No significant interference up to 25.0mg/dL

f. Method comparison with predicate device:

Correlation studies were carried out in accordance with C.L.S.I. guideline EP9-A2 'Method Comparison and Bias Estimation Using Patient Samples: Approved Guideline – Second Edition'.

106 serum patient samples spanning the range 0.21 to 26.9 mg/dL were tested by two operators on two lots of Total Bilirubin reagent on one RX Daytona plus analyzer and the predicate device tested on one ADVIA 1650 system across 3 working days with each sample tested in singlicate.

The test method was compared to the predicate device and the following linear regression equation was obtained:

Y = 1.02x – 0.02
Correlation coefficient of r = 0.9999

g. Matrix comparison:

Matrix method comparisons for Total Bilirubin assay was tested by one operator on one RX Daytona plus system and was assessed for two lots of reagents. Both serum and lithium heparin plasma were tested to determine whether method accuracy with plasma specimens are equivalent to serum results and that lithium heparin plasma does not interfere with either the method or the system.

Total Bilirubin matrix comparison on the RX Daytona plus (Lithium Heparin)

Patient samples were drawn in matched pairs – one sample serum (x) and the second sample lithium heparin plasma (y). A minimum of 40 matched patient sample pairs were analyzed spanning the 0.23 to 23.5 mg/dl and the following linear regression equation was obtained:

Y = 0.99x + 0.04

Correlation coefficient of r = 0.9999

Expected values/Reference range:

Referenced from literature

A reference interval for Total Bilirubin was verified using NCCLS C28-A3 guidelines. In a study, human serum from 30 normal donors were tested in singlicate on the RX daytona plus. The results obtained were ordered from lowest to highest before being examined for outliers using the Dixon test.

Upon confirmation there were no outliers; the values were compared to the quoted ranges for Total Bilirubin. Results of the study indicate that all values reported in the range for Healthy Individuals.

Table 4 **Reference Ranges**

Analyte	**Expected Values**
Total Bilirubin [2]	0.3 – 1.2 mg/dL

2. WuAHB. Tietz Clinical Guide to laboratory Tests, 4th edition, Saunders Elsevier, St. Louis, MO: 2006:316.

10. CONCLUSION

Testing results indicate that the proposed device is substantially equivalent to the predicate device.