DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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March 9, 2017

SIEMENS HEALTHCARE DIAGNOSTICS, INC.
JULIE WARREN
REGULATORY TECHNICAL SPECIALIST
511 BENEDICT AVENUE
TARRYTOWN NY 10591

Re: K170065
Trade/Device Name: ADVIA® Chemistry Total Bilirubin_2 (TBIL_2)
Regulation Number: 21 CFR 862.1110
Regulation Name: Bilirubin (total or direct) test system
Regulatory Class: II
Product Code: JFM, MQM
Dated: January 6, 2017
Received: January 9, 2017

Dear Julie Warren:

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,

Kellie B. Kelm -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)*
K170065

Device Name
ADVIA® Chemistry Total Bilirubin_2 (TBIL_2)

Indications for Use *(Describe)*
For in vitro diagnostic use in the quantitative determination of total bilirubin in serum and plasma of adults and neonates on the ADVIA® Chemistry systems. Measurement of total bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic hematological, and metabolic disorders, including hepatitis and gall bladder block. A total bilirubin measurement in newborn infants is intended to aid in indicating the risk of bilirubin encephalopathy (kernicterus).

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

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of Safe Medical Device Act of 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K170065

1. Submitter

Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY 10591 USA
Establishment Registration Number: 2432235
Contact Person: Julie Warren
Tel: 302-631-8722
Fax: 302-631-6299
Email: julie.warren@siemens.com

Date of Preparation: March 8, 2017

2. Device Information

Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional. For *in vitro* diagnostic use.

Name of Device:	ADVIA® Chemistry Total Bilirubin_2 (TBIL_2)
Common Name:	TBIL_2
Regulation Description:	Bilirubin (total or direct) test system; Bilirubin (total and unbound) in the neonate system
Regulation Section:	21 CFR §862.1110; 21 CFR §862.1113
Device Class:	Class II
Product Code:	JFM; MQM
Panel:	Clinical Chemistry

3. Predicate Device

Product Name:	Abbott Laboratories Total Bilirubin
510(k) Clearance	K150510
Regulation Description:	Bilirubin (total or direct) test system; Bilirubin (total and unbound) in the neonate system
Regulation Section:	21 CFR §862.1110; 21 CFR §862.1113
Device Class:	Class II
Product Code:	CIG; MQM
Panel:	Clinical Chemistry

4. Device Description

The ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) reagents are liquid ready to use. They are packaged as a kit with two kit sizes available as follows.

Kit Size – 70 mL Wedge Reagent 1 and 70 mL Reagent 2 Wedge	
Reagent 1	4 wedges x 68 mL
Reagent 2	4 wedges x 25 mL
Kit Size - 40 mL Reagent 1 and 20 mL Reagent 2 Wedge	
Reagent 1	4 wedges x 38 mL
Reagent 2	4 wedges x 13 mL

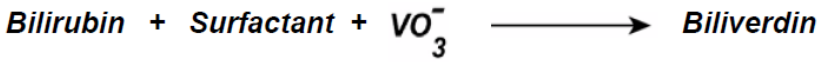
Each reagent kit consists of reagents of components and concentrations summarized below.

Reagent	Component and Concentration
Reagent 1	Citrate buffer, pH 2.9 (0.1mol/L) Detergent
Reagent 2	Phosphate buffer, pH 7.0 (10mmol/L) Sodium metavanadate (4 mmol/L)

Assay Principle

The ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) method is based on a chemical oxidation method using vanadate as an oxidizing agent. The bilirubin is oxidized by vanadate at about pH 2.9 to produce biliverdin. In the presence of the detergent and the vanadate, both conjugated (direct) and unconjugated bilirubin are oxidized. This oxidation reaction causes the decrease in the optical density of the yellow color, which is specific to bilirubin. The decrease in optical density at 451/545 nm is proportional to the total bilirubin concentration in the sample. The concentration is measured as an endpoint reaction.

Reaction Equation



5. Intended Use/Indications for Use

For *in vitro* diagnostic use in the quantitative determination of total bilirubin in human serum and plasma of adults and neonates on the ADVIA® Chemistry systems. Measurement of total bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic hematological, and metabolic disorders, including hepatitis and gall bladder block. A total bilirubin measurement in newborn infants is intended to aid in indicating the risk of bilirubin encephalopathy (kernicterus).

6. Medical Device to Which Equivalence is Claimed

The Siemens Healthcare Diagnostics Inc. ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) and the Abbott Laboratories Total Bilirubin Assay are both *in vitro* diagnostic devices intended to be used in the quantitative determination of total bilirubin in human serum and plasma. The predicate and the proposed device support the use in quantitating total bilirubin in human serum and plasma in adults and neonates. The proposed device was compared side by side to the predicate device via the following table to examine their similarities and differences between the devices.

Substantial Equivalence Comparison of Technological Characteristics with the Predicate Device

Attribute	**Predicate Device Abbott Laboratories (K150510)**	**Proposed Device ADVIA® Chemistry Total Bilirubin_2 (TBIL_2)**
Intended Use/ Indications for Use	The Total Bilirubin assay is used for the quantitation of total bilirubin in human serum or plasma of adults and neonates on the ARCHITECT c8000 System. Measurement of total bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic, hematological and metabolic disorders, including hepatitis and gall bladder block. A bilirubin (total and unbound) in the neonate test system is a device intended to measure the levels of bilirubin (total and unbound) in the blood (serum) of newborn infants to aid in indicating the risk of bilirubin encephalopathy (kernicterus).	For in vitro diagnostic use in the quantitative determination of total bilirubin in human serum and plasma on the ADVIA® Chemistry systems. Measurement of total bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic hematological, and metabolic disorders, including hepatitis and gall bladder block. A total bilirubin measurement in newborn infants is intended to aid in indicating the risk of bilirubin encephalopathy (kernicterus).
Measurand	Total Bilirubin	Same
Assay Principle	Total (conjugated and unconjugated) bilirubin couples with a diazo reagent in the presence of a surfactant to form azobilirubin. The diazo reaction is accelerated by the addition of surfactant as a solubilizing agent. The increase in absorbance at 548 nm due to azobilirubin is	The bilirubin is oxidized by vanadate at about pH 2.9 to produce biliverdin. In the presence of the detergent and the vanadate, both conjugated (direct) and unconjugated bilirubin are oxidized. This oxidation reaction causes the decrease in the optical density of the yellow color, which is specific to bilirubin. The decrease in

Attribute	Predicate Device Abbott Laboratories (K150510)	Proposed Device ADVIA® Chemistry Total Bilirubin_2 (TBIL_2)
	directly proportional to the total bilirubin concentration.	optical density at 451/545 nm is proportional to the total bilirubin concentration in the sample.
Measurement Protocol	End-point colorimetric	End-point
Sample Types	Serum and plasma from adults and neonates	Same
Reagent Form	Liquid, ready to use	Same
Reagent Composition	R1: Surfactants 10.57% HCl 6.563 g/L R2: 2,4-dichloroaniline 0.81 g/L HCl 5.563 g/L Sodium nitrite 0.345 g/L Surfactant 1.96%	R1: Citrate buffer, pH 2.9 (0.1 mol/L); Detergent R2: Phosphate buffer, pH 7.0 (10 mmol/L); Sodium metavanadate (4 mmol/L)
Measuring Range	0.3 to 25.0 mg/dL	0.15 mg/dL-35.0 mg/dL
Expected Values	<u>Premature Newborn</u> <24 hours: <8.0 mg/dL <48 hours: <12.0 mg/dL 3 to 5 days: <15.0 mg/dL 7 days: <15.0 mg/dL <u>Full Term Newborn</u> <24 hours: <6.0 mg/dL <48 hours: <10.0 mg/dL 3 to 5 days: <12.0 mg/dL 7 days: <10.0 mg/dL <u>Adults</u> 0.3 – 1.2 mg/dL	Age: 0-1 day: <8.0 mg/dL 1-2 days: <12.0 mg/dL 3-5 days: <16.0 mg/dL >5 days – 60 years: 0.3-1.2 mg/dL* 60 – 90 years: 0.2-1.1 mg/dL >90 years: 0.2-0.9 mg/dL *Ages >5 days to <29 days are neonates and >29 days to 60 years are children and adults.
Instrument	ARCHITECT c8000 System	ADVIA® Chemistry 1800 System

7. Performance Characteristics

All studies used to support the use of the device on the adult population were previously cleared under 510(k), K063845. Claims which are being transferred from the previous submission were performed on the ADVIA® Chemistry 1650 System, and therefore were not repeated. The reagent formulation and method parameters remain the same.

a. Method Comparison

A method comparison study was performed to demonstrate the accuracy of the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) on the ADVIA® Chemistry 1800 System following *CLSI EP09-A3 Measurement Procedure Comparison and Bias Estimation Using Patient Samples, Approved Guideline*, *Third Edition.* The comparative method was a legally marketed comparator method with a linearity range of 0.146 – 35.1 mg/dL. Samples were tested across the assay range. Weighted Deming regression analysis was performed. Results are summarized below.

Regression Summary

N	119
Range	0.7 – 31.6 (ADVIA®) 0.8 – 26.6 mg/dL (Comparator Method)
Slope	1.06
y-intercept	-0.24
Correlation coefficient (r)	0.990

In addition, the bias at the medical decision levels (MDL) for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) were calculated using the regression equation y = 1.06x-0.24. Medical decision point concentration (bias) is as follows: 1.0 mg/dL (-0.2 mg/dL), 8.0 mg/dL (0.2 mg/dL), 13.0 mg/dL (0.5 mg/dL), and 17.0 mg/dL (0.8 mg/dL).

b. Analytical Measuring Range/Linearity

Linearity was evaluated on the ADVIA® Chemistry 1800 System to determine the upper limit of the assay range according to *CLSI EP06-A: Evaluation of the Linearity of Quantitative Analytical Measurement Procedure: A Statistical Approach, Approved Guideline.*

Slope	**y- intercept**	**r**	**Number of Levels**	**Observed Sample Range (mg/dL)**	**Analytical Measuring Range (mg/dL)**
0.999	0.016	0.999	9	0.0-39.2	0.15-35.0

c. Limits of Detection and Quantitation

Limits of Blank (LoB) and Limit of Detection (LoD) were determined experimentally on the ADVIA® Chemistry 1800 System following *CLSI EP 17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline; Second Edition*. The limit of blank and limit of detection for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) is 0.02 mg/mL and 0.06 mg/dL, respectively.

Limit of Quantitation (LoQ) was determined experimentally following *CLSI EP05*-A2 *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline; Second Edition.* The limit of quantitation for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) is 0.08 mg/dL.

d. Interferences

Interference testing was evaluated ADVIA® Chemistry 1800 System according to *CLSI EP07-A2 Interference Testing in Clinical Chemistry, Approved Guideline, Second Edition*. Neonatal specific interferences were tested in a sample with low and high concentration of bilirubin. The following interferents tested were acceptable with ≤10% bias or recovery of interferent to blank within ±10%.

Substance	**Highest substance concentration tested that did not show significant interference**
Indican	10 mg/dL
Cyanokit	40 ug/mL
HbF	1000 mg/dL
HbA	1000 mg/dL

e. Expected Values (Reference Interval)

The reference interval for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) is outlined in the literature reference: *Wu AHB. Tietz Clinical Guide to Laboratory Tests, 4th edition, Saunders Elsevier, St. Louis, MO: 2006:172*.

The expected values were verified in accordance with *CLSI EP28-A3c Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, Approved Guideline, Third Edition*; October 19, 2010. Expected value ranges for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) are as follows.

Age	**Expected Values**
0-1 day	<8.0 mg/dL
1-2 days	<12.0 mg/dL
3-5 days	<16.0 mg/dL
>5 days – 60 years	0.3-1.2 mg/dL
60 – 90 years	0.2-1.1 mg/dL
>90 years	0.2-0.9 mg/dL

8. Conclusion

The Siemens Healthcare Diagnostics Inc. ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) were previously cleared for the adult population under 510(k), K063845. Studies on adults were not repeated because the formulation and method parameters remain the same.

The ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) and the Abbott Laboratories Total Bilirubin Assay are both *in vitro* diagnostic devices intended to be used in the quantitative determination of total bilirubin in human serum and plasma in adults and neonates. Both assays are liquid and ready to use on automated systems. Siemens Healthcare Diagnostics Inc. claims substantial equivalence to the currently marketed Abbott Laboratories Total Bilirubin Assay (K150510).