DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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January 8, 2016

ROCHE DIAGNOSTICS OPERATIONS (RDO)
BARBARA MCWHORTER
REGULATORY AFFAIRS PRINCIPAL
9115 HAGUE ROAD
INDIANAPOLIS IN 46250

Re: K152245
Trade/Device Name: ONLINE TDM Vancomycin Gen.3
Regulation Number: 21 CFR 862.3950
Regulation Name: Vancomycin test system
Regulatory Class: II
Product Code: LEH
Dated: December 9, 2015
Received: December 10, 2015

Dear Barbara McWhorter:

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,

Courtney H. Lias -S

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
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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)*
K152245

Device Name
ONLINE TDM Vancomycin Gen.3

Indications for Use *(Describe)*
In vitro test for the quantitative determination of vancomycin in serum and plasma on Roche/Hitachi cobas c systems.

A vancomycin test system is a device intended to measure vancomycin, an antibiotic drug, in serum and plasma. Measurements obtained by this device are used in the diagnosis and treatment of vancomycin overdose and in monitoring the level of vancomycin to ensure appropriate therapy.

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

Submitter Name	Roche Diagnostics Operations (RDO)
Address	9115 Hague Road Indianapolis, IN, 46250, USA
Contact	Barbara McWhorter Phone: (317) 521-2336 FAX: (317) 521-2324 Email: Barbara.McWhorter@roche.com
Date Prepared	July 31st, 2015
Proprietary Name	ONLINE TDM Vancomycin Gen.3
Common Name	Immunoassay, Vancomycin
Classification Name	Clinical Toxicology Test Systems, Class II
Product Codes	LEH, 21 CFR § 862.3950
Predicate Devices	ONLINE TDM Vancomycin, K060586
Establishment Registration	1823260, Roche Diagnostics Operations Inc.

1. DEVICE DESCRIPTION

The ONLINE TDM Vancomycin Gen.3 is a two reagent assay for the in vitro quantitative determination of vancomycin in human serum or plasma on automated clinical chemistry analyzers. It is a homogeneous microparticle agglutination immunoassay based on the kinetic interaction of microparticles in solution (KIMS). A competitive reaction takes place between the drug conjugate and vancomycin in the serum sample for binding to the vancomycin antibody on the microparticles. The resulting kinetic interaction of microparticles is indirectly proportional to the amount of drug present in the sample.

2. INDICATIONS FOR USE

In vitro test for the quantitative determination of vancomycin in serum and plasma on Roche/Hitachi **cobas c** systems.

A vancomycin test system is a device intended to measure vancomycin, an antibiotic drug, in serum and plasma. Measurements obtained by this device are used in the diagnosis and treatment of vancomycin overdose and in monitoring the level of vancomycin to ensure appropriate therapy.

3. TECHNOLOGICAL CHARACTERISTICS

The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Vancomycin antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions is induced by binding of drug‑conjugate to the antibody on the microparticles and is inhibited by the presence of Vancomycin in the sample. A competitive reaction takes place between the drug conjugate and Vancomycin in the serum sample for binding to the Vancomycin antibody on the microparticles. The resulting kinetic interaction of microparticles is indirectly proportional to the amount of drug present in the sample.

Reagents - working solutions:

- R1 Vancomycin conjugate; piperazine‑N,N'‑bis (2‑ethanesulfonic acid) (PIPES) buffer, pH 7.2; preservative; stabilizer
- R2 Anti‑Vancomycin antibody (mouse monoclonal); latex microparticle; 3‑(N‑morpholino) propane sulfonic acid (MOPS) buffer, pH 7.2; stabilizer

4. PREDICATE DEVICE

The predicate device, manufactured by Siemens, which Roche Diagnostics claims substantial equivalence to, is the ONLINE TDM Vancomycin assay. This was cleared in k060586 as a Traditional 510(k) on the Roche/Hitachi 917 and Modular P analyzer systems. The ONLINE TDM Vancomycin assay was then applied to the **cobas c** 501 analyzer system. FDA designated this CLIA categorization as moderate complexity with the k060373/A001.The following table compares the features of the candidate device to the predicate device.

Table 1: Substantial Equivalence – Assay Comparison

Assay Comparison		
Feature	**Predicate Device: ONLINE TDM Vancomycin K060586**	**Candidate Device: ONLINE TDM Vancomycin Gen.3**
Intended Use	The ONLINE TDM Vancomycin assay is for the quantitative determination of vancomycin in human serum or plasma on Roche automated clinical chemistry analyzers.	In vitro test for the quantitative determination of vancomycin in serum and plasma on Roche/Hitachi **cobas c** systems.
Analyzer Systems	Hitachi / Roche Modular P and 917 **cobas c** 501 (k060373/A001)	**cobas c** 501
Sample Types	Serum: Collect serum using standard sampling tubes. Plasma:Potassium (K_2 or K_3) EDTA,sodium citrate, or fluoride oxalate plasma.	Serum Plasma: K_2- or K_3‑EDTA, lithium heparin.

Assay Comparison		
Feature	**Predicate Device: ONLINE TDM Vancomycin K060586**	**Candidate Device: ONLINE TDM Vancomycin Gen.3**
Test Principle	The assay is based on a homogeneous enzyme immunoassay technique used for the quantitative analysis of vancomycin in human serum or plasma. The assay is based on competition between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for antibody binding sites. Enzyme activity decreases upon binding to the antibody, so the drug concentration in the sample can be measured in terms of enzyme activity. Active enzyme converts oxidized nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that is measured spectrophotometrically. Endogenous serum G6PDH does not interfere because the coenzyme functions only with the bacterial (Leuconostoc mesenteroids) enzyme employed in the assay.	The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Vancomycin antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions is induced by binding of drug-conjugate to the antibody on the microparticles and is inhibited by the presence of Vancomycin in the sample. A competitive reaction takes place between the drug conjugate and Vancomycin in the serum sample for binding to the Vancomycin antibody on the microparticles. The resulting kinetic interaction of microparticles is indirectly proportional to the amount of drug present in the sample.
Reagent Shelf Life Stability	2-8 ºC until expiration date	Same
Reagent On-Board Stability	60 days opened and refrigerated on the analyzer. Do not freeze.	12 weeks on-board in use and refrigerated on the analyzer. Do not freeze.
Measuring Range	1.7 to 80 µg/mL (based on LDL)	4.0 to 80 µg/mL (based on LoQ)
Traceability	This method has been standardized against USP reference standards.	Same
Calibrator	Preciset TDM 1 calibrator (Previously cleared 510(k): k031856)	Same
Calibration Frequency	• after reagent bottle change • after reagent lot change • as required following quality control procedures	• after lot change • after 6 weeks • as required following quality control procedures
Controls	TDM Control Set (Previously cleared 510(k): k060429 and k070200)	Same

Assay Comparison		
Feature	**Predicate Device: ONLINE TDM Vancomycin K060586**	**Candidate Device: ONLINE TDM Vancomycin Gen.3**
Lower Limits of Measurement	Lower Detection Limit = 1.7 µg/mL (1.2 µmol/L)	LoB = 1.0 µg/mL (0.69 µmol/L) LoD = 1.5 µg/mL (1.04 µmol/L) LoQ = 4.0 µg/mL (2.76 µmol/L)
Reagent Composition	R1 Enzyme Reagent Vancomycin labeled with bacterial G6PHDH in buffer R2 Antibody/Substrate Reagent Anti-vancomycin antibody (mouse monoclonal), G6P and NAD in buffer	R1 Vancomycin conjugate; piperazine-N,N'-bis (2 ethanesulfonic acid) (PIPES) buffer, pH 7.2; preservative; stabilizer R2 Anti‑Vancomycin antibody (mouse monoclonal); latex microparticle; 3-(N‑morpholino) propane sulfonic acid (MOPS) buffer, pH 7.2; stabilizer

5. NON-CLINICAL PERFORMANCE EVALUATION

The following performance data were provided in support of the substantial equivalence determination:

Detection Limit: LoB, LoD and LoQ according to CLSI EP17-A2

Precision according to CLSI EP5-A2

Linearity according to CLSI EP6-A

Matrix Comparison - Anticoagulants

Interferences - H, L and I Indices

Interference - Drugs

Method Comparison to Predicate

5.1. Detection Limit

LoB, LoD, and LoQ studies were performed based upon CLSI EP17-A2.

LoB:

LoB (Limit of Blank) corresponds to the concentration below which analyte‑free samples are found with a probability of 95%.

For MP Lot: The diluent is measured with 5-fold determinations per run on two instruments. Six runs distributed over 3 days were performed. Data analysis was based on determination of the 95th percentile of the 60 measured values.

For P2 and P3 Lots: The diluent is measured with 5-fold determinations per run on one instrument. Six runs distributed over 3 days were performed. Data analysis was based on determination of the 95th percentile of the 60 measured values.

LoD:

LoD (Limit of Detection) corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

For MP Lot: Five serum samples with low analyte content spiked with Vancomycin (with concentrations ranging from LoB to approx. 4 times specified LoB) were measured with 1-fold determination per run on two instruments. Six runs distributed over 3 days were performed.

For P2 and P3 Lots: Five serum samples with low analyte content spiked with Vancomycin (with concentrations ranging from LoB to approx. 4 times specified LoB) were measured with 2-fold determination per run on one instrument. Six runs distributed over 3 days were performed.

LoQ:

LoQ (Limit of Quantitation) is the lowest amount of analyte in a sample that can be detected quantitatively within specified precision and accuracy ranges.

Fifteen serum samples were prepared which cover the concentration range between LoB and 2x LoQ. Those samples were tested in two aliquots. Six runs over 4 days were performed.

Expected value is determined with Vancomycin LCMS/MS.

Table 2: LoB, LoD, and LoQ Experimental Determination

	Result MP Lot (µg/mL)	Result P2 Lot (µg/mL)	Result P3 Lot (µg/mL)	Claim (µg/mL)
Limit of Blank (LoB)	0.6	0.7	0.5	1.0
Limit of Detection (LoD)	1.4	1.3	1.1	1.5
Limit of Quantitation (LoQ)	2.0	3.3	3.1	4.0

5.2. Precision according to CLSI EP5-A

Precision experiments were performed in Accordance with CLSI Guideline EP5-A2. Two runs per day for ≥ 21 days were performed on the same analyzer. Repeatability and intermediate precision was calculated. The serum samples were randomized in each run separately. The data set was completed for the 21 days. For each sample, the following were calculated: Mean, Repeatability and Intermediate precision as CV and SD values.

Table 3: Repeatability Precision Summary

Specimen	Mean (µg/mL)	SD (µg/mL)	CV (%)
TDM Control 1	7.45	0.4	5.2
TDM Control 2	21.5	0.5	2.3
TDM Control 3	36.2	0.9	2.4
Human Serum 1	4.82	0.4	8.2
Human Serum 2	7.95	0.4	5.2
Human Serum 3	32.1	0.8	2.5
Human Serum 4	40.0	1.0	2.5
Human Serum 5	71.4	2.0	2.8

Table 4: Intermediate Precision Summary

Specimen	Mean (µg/mL)	SD (µg/mL)	CV (%)
TDM Control 1	7.45	0.5	6.2
TDM Control 2	21.5	0.8	3.7
TDM Control 3	35.5	1.1	3.2
Human Serum 1	4.93	0.5	10.5
Human Serum 2	7.95	0.5	5.9
Human Serum 3	32.1	1.1	3.4
Human Serum 4	39.5	1.1	2.9
Human Serum 5	71.4	2.2	3.1

5.3. Linearity according to CLSI EP6-A

A dilution series were prepared from a human serum sample pool and diluent (Preciset TDM1Diluent). The dilution series were prepared to obtain sixteen levels* (including the high concentration pool and diluent). The diluted samples shall span the measuring range including a non-zero sample below the measuring range and a sample over the measuring range. The process was repeated for plasma samples.

* Due to the importance of the trough concentration (ca. 5 – 10 µg/mL Vancomycin) and due to the unknown LoQ before the measurement, more samples were chosen in the low concentration range.

The calculation is according to the CLSI guideline EP6-A. All measurement data of the dilution steps were calculated by linear regression without weighting.

Table 5: Linearity Results

Sample Type	Linear Regression Equation	Claimed Measuring Range
Serum	y=1.000x-0.000 Pearson correlation coefficient (R)=0.9985	4.0 to 80.0 µg/mL
Plasma	y=1.000x-0.000 Pearson correlation coefficient (R)=0.9976	4.0 to 80.0 µg/mL

5.4. Matrix Comparison - Anticoagulants

Each pair of serum and plasma of a single donor are spiked with Vancomycin. Included in the data are 67 full tubes and 9 half-filled tubes (except K2-EDTA plasma, which had 10 tubes). The half-filled and filled sample tubes are also from one donor. Method comparison is executed by taking the serum as reference. Only samples within the measuring range were used.

The following method comparisons are provided:

- K2-EDTA plasma vs serum
- K3-EDTA plasma vs serum
- Li-Heparin plasma vs serum

Table 6: Matrix Comparison

Anticoagulant	Correlation
Serum vs. Li-heparin	y = 1.01x -0.3, r = 0.996
Serum vs. K2-EDTA	y = 0.99x -0.0, r = 0.996
Serum vs. K3-EDTA	y = 1.00x - 0.3, r = 0.995

5.5. Interferences - H, L and I Indices

The effect on quantitation of analyte in the presence of endogenous interfering substances is determined at two Vancomycin concentrations and a dilution set of the added interfering substances. Interfering substances evaluated include:

Hemolysis up to an H index of 1000

Lipemia up to an L index of 1000

Icterus/Bilirubin up to an I index of 60

High concentrated stock solutions of the interference substances were prepared in a suitable solvent. Two human serum sample pools were spiked with the defined Vancomycin concentrations and divided into two aliquots. The potential interfering substance is added to one aliquot, while the other aliquot was mixed with the same amount of solvent without the interfering substance. A dilution series was prepared with 11 dilution steps for each interferent by mixing the 2 aliquots. Three aliquots per level were tested in 1 run on 1 instrument and 1 lot.

The parts containing the interfering substance will have the same Vancomycin concentrations as the aliquots containing no interfering substance. When diluting those two aliquots the Vancomycin concentration will remain constant while the concentration of interferent will vary. Thus the effect of increasing concentrations of interferent can be determined.

Median of the measured results were compared to the expected result (aliquot with no interfering substance) and the recovery is determined (paired difference testing).

Table 7: Interference from Endogenous Substances

Interferent	No interference up to
Hemolysis	Level 1: 1161 H Index Level 2: 1133 H Index
Lipemia	Level 1: 1234 L Index Level 2: 1232 L Index
Unconjugated Bilirubin	Level 1: 79 I Index Level 2: 82 I Index
Conjugated Bilirubin	Level 1: 77 I Index Level 2: 75 I Index

Labeling Claim for Endogenous Substances:

Icterus:

No significant interference up to an I index of 60 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:

No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 622 µmol/L).

Lipemia (Intralipid):

No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration. No significant interference from triglycerides up to 1000 mg/dL (11.4 mmol/L).

5.6. Interferences – Drugs

Two human serum sample pools spiked with the defined Vancomycin concentrations were divided into two aliquots. One aliquot of each concentration were used as the reference sample for Vancomycin concentration and were not spiked with the drugs but the solvent for the drug.

The other aliquots, with either the high or low Vancomycin concentration, were spiked with the respective amount of drug. The Vancomycin concentration of the spiked aliquots were tested with 3 replicates in one run, 1 reagent lot and one instrument. The defined pharmaceutical compounds were spiked into samples with concentrations according to EP7-A2 or higher concentrations.

Table 8: Common Drug Interferences

Drug	Highest Concentration Shown Not to Interfere with Vancomycin
Acetylsalicylic acid	1000 mg/L
Acetaminophen	200 mg/L
Acetylcysteine	1660 mg/L
Ampicillin-sodium	1000 mg/L
Ascorbic acid	300 mg/L
Cefoxitin	2500 mg/L
Cyclosporine	5 mg/L
Doxycycline	50 mg/L
Heparin	5000 U/L
Ibuprofen	500 mg/L
Levodopa	20 mg/L
Methyldopa	20 mg/L
Metronidazole	200 µg/mL
Methotrexate	455 µg/mL
Phenylbutazone	400 mg/L
Rifampicin	60 mg/L
Theophyllin	100 mg/L

5.7. Method Comparison to Predicate

One hundred twenty five single native human serum samples of patients taking Vancomycin covering the reportable range were tested. Eight of these native Vancomycin samples were spiked with Vancomycin and 1 sample diluted to cover the range. All samples were tested for icteric, lipemic and hemolytic interference.

The samples were tested in singlicate on the candidate and predicate device (**cobas c** 501).

The data was evaluated using Passing Bablok Regression analysis.

$$y = 0.993x + 0.641, r = 0.994$$

6. CONCLUSIONS

The submitted information in this premarket notification supports a substantial equivalence decision.