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

**A. 510(k) Number:**
k060586

**B. Purpose for Submission:**
New Device

**C. Measurand:**
Vancomycin

**D. Type of Test:**
Homogeneous Enzyme Immunoassay

**E. Applicant:**
Roche Diagnostics Corp.

**F. Proprietary and Established Names:**
Roche Diagnostics ONLINE TDM Vancomycin Assay

**G. Regulatory Information:**

1. Regulation section:
   21 CFR 862.3950
2. Classification:
   Class II
3. Product Code:
   LEH
4. Panel:
   Toxicology (91)

**H. Intended Use:**

1. Intended use(s):
   Refer to Indications for Use

2. Indication(s) for use:
   The ONLINE TDM Vancomycin assay is for the quantitative determination of vancomycin in human serum or plasma on Roche automated clinical chemistry analyzers. 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. Special conditions for use statement(s):
   The device is for in vitro diagnostic use.

It is intended for prescription use only.

4. Special instrument requirements:
   Roche/Hitachi 911, 912, 917, and MODULAR P analyzers

**I. Device Description:**

The ONLINE TDM Vancomycin assay consists of 2 wet reagents that contain glucose-6-phosphate dehydrogenase (G6PDH) labeled vancomycin, mouse monoclonal anti-vancomycin antibodies, NAD, glucose-6-phosphate (G6P), and buffers.

Calibrators for this assay include the Preciset TDMI Calibrator. The recommended control material for this assay is the TDM Control Set, or other commercially available suitable control material.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):
   Roche COBAS INTEGRA Vancomycin assay

2. Predicate K number(s):
   k954992

3. Comparison with predicate:
   Both devices are for the quantitative measurement of vancomycin in the same matrices and both are for use on automated analyzers.

   The reagent formulations vary between the two devices.

| Similarities | | |
|---|---|---|
| **Item** | **Device** | **Predicate** |
| Intended Use | Quantitative measurement of vancomycin | Same |
| Measuring Range | 1.7 – 80 µg/mL | 1.4 – 80 µg/mL |
| Matrix | Serum or plasma | Same |
| Storage | 2 – 8° C | Same |

| Differences | | |
|---|---|---|
| **Item** | **Device** | **Predicate** |
| Methodology | Homogeneous enzyme immunoassay | Fluorescence polarization |
| Instrumentation | Roche/Hitachi 911, 912, 917, and MODULAR P analyzers | Roche COBAS Integra |

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

1. CLSI EP5-T2: Evaluation of precision performance of clinical chemistry devices - Second Edition; Tentative Guideline, 1992

2. Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy

**L. 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 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.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

*a. Precision/Reproducibility:*

The sponsor performed a within run precision study using low, middle, and high level vancomycin controls, and low and high human serum pools (HSP). Each level was assayed twenty-one times. The concentrations used were:

| | Value (µg/mL) |
|---|---|
| TDM Control I | 6.0 |
| TDM Control II | 19.7 |
| TDM Control III | 37.3 |
| Low HSP | 15 |
| High HSP | 60 |

The sponsor's acceptance criteria were:

For concentrations up to 10 µg/mL, standard deviation ≤ 0.9
For concentrations between 10 and 40µg/mL, CV ≤ 8%
For concentrations greater than 40µg/mL, CV ≤ 12%

All of these criteria were met for this study.

The sponsor also performed a second precision study based on CLSI document EP5-T2, which addresses within-run, total, and between-day precision. The samples used and the acceptance criteria were the same as with the within-run precision study above.

Three replicate measurements of each sample were analyzed in one run per day over 21 days. Four calibrations were performed during the course of the study.

| Specimen | Control I | Control II | Control III | Low HSP | High HSP |
|---|---|---|---|---|---|
| Total Mean | 6.80 | 21.01 | 39.06 | 16.41 | 62.38 |
| Within Run precision SD | 0.3357 | 0.2930 | 0.4481 | 0.2696 | 0.8103 |
| Within Run precision CV% | 4.9% | 1.4% | 1.1% | 1.6% | 1.3% |
| Total precision SD | 0.3967 | 0.6005 | 1.0391 | 0.6647 | 2.5380 |
| Total precision CV% | 5.8% | 2.9% | 2.7% | 4.1% | 4.1% |
| Between-day precision SD | 0.2114 | 0.5242 | 0.9375 | 0.6075 | 2.4051 |
| Between-day precision CV% | 3.1% | 2.5% | 2.4% | 3.7% | 3.9% |

All of the sponsor's acceptance criteria were met for the study based on CLSI EP5-T2.

b. *Linearity/assay reportable range*:
The measuring range of the assay is 1.7 – 80 µg/dL vancomycin.

To assess the linearity of the assay, an 11-level dilution series was prepared using a vancomycin spiked human serum pool diluted with a nonspiked serum pool.
For values above 10 µg/mL, the acceptance criterion is recovery within +/- 10% of the theoretical value.

The sponsor's linearity claim extends to 80 µg/mL at the high end.

| % High Sample | Theoretical Value(µg/mL) | Assayed Value (µg/mL) | % Recovery | Recovery exceeds limit? |
|---|---|---|---|---|
| 100.0 | 111.9 | 106.5 | 95.2 | Outside measuring range |
| 90.0 | 100.7 | 100.2 | 99.5 | Outside measuring range |
| 80.0 | 89.5 | 84.0 | 93.8 | Outside measuring range |
| 70.0 | 78.3 | 75.3 | 96.1 | No |
| 60.0 | 67.1 | 64.4 | 95.9 | No |
| 50.0 | 56.0 | 55.0 | 99.9 | No |
| 40.0 | 44.8 | 42.8 | 95.6 | No |
| 30.0 | 33.6 | 34.3 | 102.2 | No |
| 20.0 | 22.4 | 23.1 | 103.2 | No |
| 10.0 | 11.2 | 11.2 | 100.1 | No |
| 0.0 | 0 | 0 | 0 | Outside measuring range |

The sponsor performed an additional linearity study using concentrations less than 10 µg/mL. At these concentrations, the sponsor's acceptance criteria are recovery within ±15% or ± 0.7µg/mL, whichever is greater.

| % High Sample | Theoretical Value(µg/mL) | Assayed Value | % Recovery | Difference in concentration | Recovery exceeds limit? |
|---|---|---|---|---|---|

| | | (µg/mL) | | units (µg/mL) | |
|---|---|---|---|---|---|
| 100.0 | 8.17 | 8.80 | 107.76 | 0.63 | No |
| 90.0 | 7.35 | 7.50 | 102.04 | 0.15 | No |
| 80.0 | 6.53 | 6.80 | 104.08 | 0.27 | No |
| 70.0 | 5.72 | 5.90 | 103.21 | 0.18 | No |
| 60.0 | 4.90 | 4.80 | 97.96 | -0.1 | No |
| 50.0 | 4.08 | 3.70 | 90.61 | -0.38 | No |
| 40.0 | 3.27 | 3.20 | 97.96 | -0.07 | No |
| 30.0 | 2.45 | 2.00 | 81.63 | -0.45 | No |
| 20.0 | 1.63 | 1.50 | -------- | -------- | Outside measuring range |
| 10.0 | 0.82 | 0.10 | -------- | -------- | Outside measuring range |
| 0.0 | 0 | 0 | -------- | -------- | Outside measuring range |

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Preciset TDM I Calibrators are prepared to contain known quantities of vancomycin in normal human serum and are traceable to USP reference standards. The calibrators were cleared under k031856. The TDM Control Set contains liquid controls based on human serum and are traceable to USP reference standards. The controls were cleared under k060429.

d. *Detection limit:*
The detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the lowest standard (standard 1 + 2SD, within-run precision, n = 21).
The calculated detection limit is 1.7 µg/mL (1.2 µmol/L).

e. *Analytical specificity:*
The specificity of the assay was calculated according to the following formula:

If Da-Dt < LDL claim, then ND (Not Detectable)

If Da-Dt > LDL claim, then the cross-reactivity is calculated as follows:

% Cross-Reactivity = [(Da-Dt)/ C] x 100

Explanation of abbreviations:
LDL = Lower Detectable Limit
Dt = Concentration of Control Analyte Spike in serum
Da = Concentration of (Analyte + Cross-Reactant)
C = Concentration of Cross-Reactant
The materials used for cross reactivity testing included the following:

| Potential Cross Reactant | Concentration Tested (µg/mL) |
|---|---|
| Acyclovir | 25 |
| Amikacin | 100 |
| Amphoteracin B | 20 |
| Aztreonam | 200 |
| Caffeine | 2 |
| CDP-1 (Vancomycin metabolite) | 20 |
| Cefazoline | 500 |
| Cefotaxine | 1000 |
| Chloramphenicol | 100 |
| Ciprofloxacin | 10 |
| Cisplatin | 25 |
| Clindamycin | 10 |
| Cyclosporine | 50 |
| Digoxin | 0.006 |
| Epinephrine | 1 |
| Erythromycin | 5 |
| Ethacrynic Acid | 50 |
| Flucytosine | 100 |
| Furosemide | 100 |
| Fusidic Acid | 500 |
| Gentamicin sulfate | 100 |
| Imipenem | 70 |
| Methicillin | 500 |
| Metronidazole | 50 |
| Netillimicin | 100 |
| Penicillin G | 10 |
| Pentamidine | 0.7 |
| Phenobarbital | 40 |
| Rifamipin | 500 |
| Salicylate | 60 |
| Sulfmethoxazole | 600 |
| Theophylline | 20 |
| Tobramycin | 100 |
| Trimethoprim | 25 |

The effects of the metabolites, cross-reactive substances, and structurally related or potentially co-administered compounds on vancomycin determination were evaluated on the Hitachi 917. Normal human serum pool was spiked with vancomycin at 25 µg/mL and the tested substance at the level listed above. Each sample prepared was run in duplicate with the

vancomycin test system and the mean value was used to determine the % cross reactivity.

There was no cross reactivity for all compounds tested at the listed concentrations.

The sponsor performed a separate drug interference study. Aliquots of a human serum pool were spiked with Vancomycin at 30 µg/mL and then further spiked with the drugs listed below. The sponsor states that all the drugs were spiked at a concentration greater than the maximum allowed daily dose. The samples were run in triplicate and the median value was compared to the target concentration of 30 µg/mL. The sponsor's acceptance criteria for each drug was within ± 10% of the targeted concentration of 30 µg/mL. All of the drugs tested met these criteria.

| Drug |
|---|
| |
| Acetylcysteine |
| Ampicillin-Na |
| Ascorbic acid |
| *K-Dobesilate |
| Cyclosporine |
| Cefoxitin-Na |
| Heparin |
| **Levodopa |
| Methyldopa + 1,5 |
| Metronidazole |
| Phenylbutazone |
| Doxycycline HCl |
| Acetylsalycilic acid |
| Rifampicin |
| Acetaminophen |
| Ibuprofen |
| Theophylline |

* hydroquinoesulfonic acid potassium salt
**L-3,4-Dihydrophenylalanine

The sponsor also analyzed the effects of bilirubin, hemoglobin, lipemia (using Intralipid), rheumatoid factor, and total protein on the assay. Vancomycin was spiked into normal human serum at concentrations of 20 and 50 µg/mL for bilirubin, hemoglobin, and lipemia. For rheumatoid factor and total protein vancomycin was spiked in at 25 µg/mL only. Increasing amounts of bilirubin, hemoglobin, Intralipid, rheumatoid factor, and total protein were added to the spiked samples and analyzed in triplicate. The median value was chosen for

comparison for all the compounds except total protein where the mean was used. The sponsor's acceptance criterion was a recovery within ±10% of the targeted concentrations of 20, 25 and 50 µg/mL. Although higher concentrations of the interferents caused no interference, in their labeling the sponsor makes the following claims:

No interference from:

Bilirubin (icterus) up to 30 mg/dL
Hemoglobin up to 650 mg/dL
Triglycerides (lipemia) up to 500 mg/dL
Rheumatoid Factor up to 100 IU/mL
Total Protein up to 12 g/dL

The sponsor included this statement in their labeling regarding human anti-mouse antibodies (HAMA): As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample, which could cause falsely lowered results.

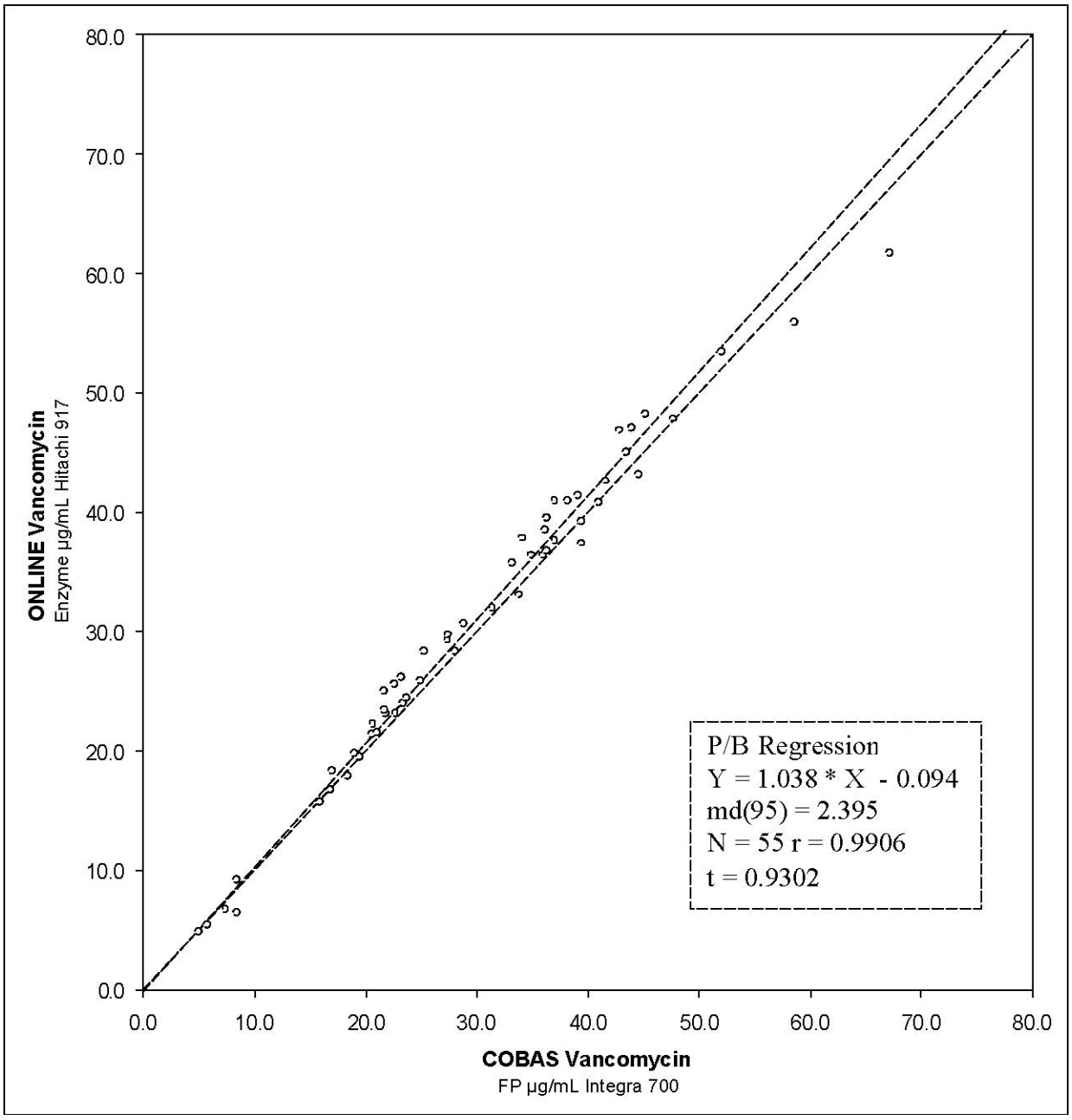
For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

*f. Assay cut-off:*
Not Applicable.

2. Comparison studies:

*a. Method comparison with predicate device:*
Fifty five non-pooled human samples were assayed in singlicate in 1 run vs. the COBAS FP vancomycin reagent on the COBAS INTEGRA 700 analyzer. The samples ranged in concentration from 5.0 to 67.2 µg/mL**.** The testing was performed at Roche Diagnostics.

The sponsor's acceptance criteria for the Passing-Bablok regression statistics are a slope of 1.00 ± 0.10 (0.90-1.10), a correlation coefficient (r) of 0.95 or greater, and a y-intercept of ± 0.27 µg/mL. The actual results obtained were a slope of 1.038, a correlation coefficient (r) of 0.99, and a y-intercept of 0.094 µg/mL. The sponsor provided a regression plot of the method comparison.




*b. Matrix comparison:*
The sponsor provided comparison data demonstrating comparable results between serum and plasma from K2/K3 EDTA, sodium citrate, and fluoride oxalate collection tubes.

3. Clinical studies:
   *a. Clinical Sensitivity:*
   Not Applicable
   *b. Clinical specificity:*
   Not Applicable. Clinical studies are not typically submitted for this device type.
   c. *Other clinical supportive data (when a. and b. are not applicable):*

4. Clinical cut-off:
   Not Applicable.
5. Expected values/Reference range:
   The sponsor claims expected vancomycin trough values of 5 – 10 µg/mL and peak values of 25 – 40 µg/mL. These values were obtained from published literature.

**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.