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

A. 510(k) Number:

k160202

B. Purpose for Submission:

Addition of a turbidimetric Vancomycin assay to the Trinidad CH System instrument

C. Measurand:

Vancomycin

D. Type of Test:

Quantitative Immunoassay, turbidimetric

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Trinidad CH Vancomycin (Vanc) Assay

Trinidad CH Drug 3 Calibrator (DRUG3 CAL)

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.3950; Vancomycin test system

   21 CFR 862.3200; Clinical Toxicology Calibrator

2. Classification:

   Class II

3. Product code:

   LEH, DLJ

4. Panel:

   Toxicology (91)

H. Intended Use:

1. Intended use(s):

   See Indications for Use below

2. Indication(s) for use:

   The Trinidad CH Vancomycin (Vanc) assay is for in vitro diagnostic use in the quantitative measurement of vancomycin in human serum or plasma on the Trinidad CH System. Vanc test results may be used in the diagnosis and treatment of vancomycin overdose and in monitoring levels of vancomycin to ensure appropriate therapy.

   The Trinidad CH Drug 3 Calibrator (DRUG3 CAL) is intended for in vitro diagnostic use in the calibration of Vancomycin (Vanc) on the Trinidad CH System.

3. Special conditions for use statement(s):

   For in vitro diagnostic use only

   For professional use only

4. Special instrument requirements:

   Trinidad CH System

I. Device Description:

The Trinidad CH Vancomycin (Vanc) assay is a turbidimetric assay previously cleared for use on the dimension clinical chemistry system in K963267. The Trinidad CH System instrument was previously cleared in k151767, but has not previously been cleared for use with any turbidimetric assays.

The Trinidad CH Vancomycin (Vanc) assay is a two reagent assay provided in reagent packs each contains two reagent wells. The contents of the reagent packs are the following:

- Vancomycin P1: Well 1, Particle Reagent 2.5 g/L; Well 2, Buffer 25.7 mM
- Vancomycin P2: Well 1: Antibody 0.034 g/L; Well 2, empty.

The Trinidad CH Drug 3 Calibrator is a five level product. The saleable device is packaged with 2 vials of each level in a box. The vials are amber borosilicate glass with

resealable polypropylene caps. The fill volume target is 5.1 mL.

Controls are not provided. The sponsor recommends the use of commercially available controls for the assay.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dimension® VANC Flex®reagent Cartridge
   Dimension Drug Calibrator II

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

   k963267; k033809

3. Comparison with predicate:

Item	Candidate Device Trinidad CH Vancomycin (VANC)	Predicate Device Dimension® VANC Flex® reagent Cartridge (k963267)
Similarities		
Intended Use	For in vitro diagnostic use in the quantitative measurement of Vancomycin in human serum or plasma.	Same
Methodology	Homogeneous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique.	Same
Assay composition	Mouse monoclonal antibody, Particle reagent, buffer	Same
Specimen type	Serum and Lithium-Heparin plasma	Same
Traceability	Traceable to USP reference standards	Same
Differences		
Measuring range	3.0–50.0 µg/mL	0.0 – 50.0 µg/mL
Instrumentation	Trinidad CH System	Cleared to be used on dimension clinical chemistry system
Calibrators	Trinidad CH Drug 3 Calibrator	Dimension Drug Calibrator II

Item	Candidate Device Trinidad CH Drug 3 Calibrator (DRUG3 CAL)	Predicate Device Dimension Drug Calibrator II (k033809)
Similarities		
Intended Use	For Vancomycin assay calibration	For calibration of multiple drug assays, including vancomycin
Calibrator Matrix:	Bovine Serum Base	Same
Levels	5	Same
Target Values	1.0, 6.6, 12.5, 25.0, 52.5 μg/mL	Same
Differences		
Drugs	Vancomycin only	Multi-drug calibrators including Vancomycin

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

- CLSI EP5-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline- Third Edition
- CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.
- CLSI EP17-A: Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline.
- CLSI EP7-A2: Interference Testing in Clinical Chemistry: Approved Guideline- Second Edition
- CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples: Approved Guideline- Second Edition

L. Test Principle:

The Trinidad CH Vancomycin (Vanc) assay is based on a homogeneous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique which uses a synthetic particle-vancomycin conjugate (PR) and monoclonal vancomycin specific antibody (Ab). Vancomycin present in the sample competes with vancomycin on the particles for available antibody, thereby decreasing the rate of aggregation. Hence, the rate of aggregation is inversely proportional to the concentration of vancomycin in the sample. The rate of aggregation is measured using bichromatic turbidimetric readings at 545 nm and 694 nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:
   Precision (within-run precision) and intermediate precision (between-day precision) were assessed in accordance with CLSI Guideline EP5-A3 using

commercial quality control material (serum based), or pooled serum and plasma samples at five different Vancomycin levels. Samples were run in duplicate, twice per day, for 20 days, on a single analyzer using 1 lot of reagent.

Sample	N	Mean (µg/mL)	Within-Run Precision		Between-Day Precision	
			SD (µg/mL)	CV(%)	SD (µg/mL)	CV(%)
Serum QC	80	6.4	0.16	2.6	0.18	2.7
Serum	80	11.2	0.20	1.8	0.23	2.0
Serum QC	80	17.5	0.28	1.6	0.35	2.0
Serum	80	32.7	0.46	1.4	0.67	2.0
Plasma	80	45.8	0.78	1.7	0.83	1.8

b. Linearity/assay reportable range:

Linearity was evaluated with 10 samples which spanned the assay measuring interval (0.9, 3.0, 7.2, 13.5, 19.7, 26.0, 32.3, 38.6, 44.8, 51.1 µg/mL). Each was prepared by mixing high and low concentration samples across the measurement interval as described in CLSI EP06-A. The high sample was prepared by spiking native serum with purified Vancomycin Hydrochloride. The low sample was normal human serum with low level of Vancomycin. Six replicates were measured for each sample. The mean of these replicates was used for the regression analysis.

The result of the liner regression is:
y=1.009x-0.16545, r=1.02

The results support the claimed measuring range of 3.0-50 µg/mL.

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

Traceability
The Trinidad CH Drug 3 Calibrator is traceable to USP Vancomycin.

Calibrator Stability
Protocols and acceptance criteria for the stability studies were reviewed and found acceptable. The real-time study results support open-vial/on board stability of 15 days at 2-8°C. Real time closed-vial stability studies are ongoing to support a shelf-life of 12 months or longer at 2-8°C.

Expected Values
Value assignment for Trinidad CH Drug 3 Calibrators will be conducted as for the predicate device cleared in K033809.

d. Detection limits:

Analytical sensitivities were determined following EP17-A2 using the nonparametric approach.

To determine LoB, 4 analyte-free samples (bovine serum base) were tested in replicate of 5 per run, with one run per day for 3 days, for a total of 60 measurements using each reagent lot (3 reagent lots were tested). The sponsor defined LoB as the concentration below which analyte-free samples could be found with a probability of 95%.

To determine LoD, 4 serum samples with low-analyte concentrations (0.1-0.3 µg/mL) were tested in replicate of 5 per run, with one run per day for 3 days, for a total of 60 measurements using each reagent lot (3 reagent lots were tested).The sponsor defined LoD as the lowest analyte concentration which could be detected, with a value above the LoB, with a probability of 95%.

To verify the claimed LoQ of 3.0 µg/mL, 4 serum samples with Vacomycine concentration of 2.5 µg/mL were tested using three reagent lots for three days, on one instrument for a total of 180 measurements. The acceptance criteria for LoQ were that the total error at the tested analyte concentration should be less than 20%.

The results are summarized in the table below and support the claimed LoB, LoD and LoQ.

	LoB (µg/mL)	**LoD (µg/mL)**	**LoQ (µg/mL)**
Lot 1	0.1	0.16	2.51
Lot 2	-0.1	0.17	2.37
Lot 3	0.1	0.19	2.77
Claimed	**0.1**	**0.2**	**3.0**

e. Analytical specificity:

Interference

The sponsor tested the effects of common endogenous substances and therapeutic compounds using human serum pools at both low (10µg/mL) and high (40µg/mL) Vancomycin levels. The % difference between the test sample and the control sample was calculated. The sponsor defined no significant interference as within a ±10% difference relative to the control sample.

No interference was detected for hemolysis, icterus and lipemia at the following concentrations: Hemoglobin 600 mg/dL, Conjugated Bilirubin 20 mg/dL, Unconjugated Bilirubin 20 mg/dL, Lipemia (Intralipid) 1000 mg/dL.

No interference was detected from the following therapeutic and endogenous substances at the indicated concentrations:

Substance	**Highest Concentration at which no significant interference was detected**	
Acetaminophen	20	mg/dL
Acetylsalicylic Acid	50	mg/dL
Amikacin	100	µg/mL
Amobarbital	10	mg/dL
Ampicillin	5	mg/dL
Ascorbic Acid	3	mg/dL
Caffeine	10	mg/dL
Carbamazepine	12	mg/dL
Cefazolin	500	µg/mL
Cefotaxime	1000	µg/mL
Chloramphenicol	100	µg/mL
Chlordiazepoxide	2	mg/dL
Chlorpromazine	5	mg/dL
Cimetidine	10	mg/dL
Clindamycin	300	µg/dL
Codeine	10	mg/dL
Creatinine	30	mg/dL
Dextran 40	6000	mg/dL
Dextran 70	2500	mg/dL
Diazepam	4	mg/dL
Digoxin	5	ng/dL
Erythromycin	20	mg/dL
Ethanol	350	mg/dL
Ethosuximide	30	mg/dL
Furosemide	2	mg/dL
Fusidic Acid	500	µg/mL
Gentamicin	12	mg/dL
Heparin (Porcine)	8000	U/L
Ibuprofen	40	mg/dL
Lidocaine	6	mg/dL
Lithium	3.5	mg/dL

Methicillin	500	µg/mL
Netilmicin	500	µg/mL
Nicotine	2	mg/dL
Penicillin V	80	mg/dL
Pentobarbital	10	mg/dL
Phenobarbital	15	mg/dL
Phenytoin	10	mg/dL
Primidone	10	mg/dL
Propoxyphene	0.4	mg/dL
Protein-Albumin	12	g/dL
Protein-IgG	5	g/dL
Protein–Total	12	g/dL
Rheumatoid Factor	1465	U/mL
Rifampin	50	µg/mL
Salicylic Acid	50	mg/dL
Secobarbital	5	mg/dL
Sodium Fluoride	1	mg/dL
Sulfamethoxazole	25	µg/mL
Theophylline	25	mg/dL
Tobramycin	100	µg/mL
Trimethoprim	25	µg/mL
Urea	500	mg/dL
Uric Acid	20	mg/dL
Valproic Acid	50	mg/dL

Cross Reactivity

Vancomycin crystalline degradation product (CDP-1) was tested for cross-reactivity at 0 and 10 µg/mL of vancomycin following CLSI document EP07-A2. The results are summarized in the below table.

Cross reactant	Test Concentration	Cross-reactivity	
	µg/mL	0.0 µg/mL Vancomycin	10 µg/mL Vancomycin
CDP-1	20	21.0%	19.1%
CDP-1	15	20.8%	18.9%
CDP-1	10	20.5%	19.5%
CDP-1	5	22.0%	19.0%

In the labeling, the sponsor states:

A number of substances cause physiological changes in serum or plasma analyte concentrations. A comprehensive discussion of possible interfering substances, their serum or plasma concentrations, and their possible physiological involvements is beyond the scope of this document. Consult the listed reference for specific details on known potential interfering substances.[6]

As with any chemical reaction, you must be alert to the possible effect on results of unknown interferences from medications or endogenous substances. The laboratory and physician must evaluate all patient results in light of the total clinical status of the patient.

Vancomycin crystalline degradation product (CDP-1) at 20 µg/mL CDP-1 demonstrates cross-reactivity at 0 and 10 µg/mL Vanc of 21.0% and 19.1% respectively.

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:
The sponsor tested 100 human serum samples (98 were native, 2 were altered) from patients taking Vancomycin, ranging in concentration from 4.4 to 48.1 µg/mL. The samples were tested in singlicate using the candidate and predicate device and analyzed using Passing Bablok regression which yielded the following regression equation: y = 1.04x -1.04, r = 0.997.

b. Matrix comparison:
A matrix comparison study between serum and Lithium-Heparin plasma was performed using 60 matched samples with Vancomycin concentrations from 4.0 to 43.3 µg/mL. The equation produced from linear regression analysis was:
y=1.00x+0.49, r=0.990

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:

In the labeling, the sponsor states:

The therapeutic intervals are cited from the literature [1,2]:

There is great disparity in vancomycin therapeutic intervals, especially with peak therapeutic intervals. Factors that might affect peak therapeutic ranges include dosage regimen and timing of sample collection.

Vancomycin levels in renal dialysis patients, burn patients and intravenous drug abusers should be closely monitored.

Peak Intervals: Samples from adult volunteers drawn two hours after the completion of a 60 minute infusion of vancomycin ranged from 18 – 26 μg/mL. Samples drawn one hour after the completion of a 60 minute vancomycin infusion ranged from 25 – 40 μg /mL. Samples drawn 30 minutes after the completion of a 60 minute infusion of vancomycin ranged from 30 – 40 μg/mL.

Trough Intervals: Samples should be drawn just before the next dose. A trough interval of 5–10 μg/mL (3.5–6.9 μmol/L) is generally considered to be effective; however, therapeutic levels should be established based on individual patient differences, clinical assessment, and bacterial susceptibility.

As with all in vitro diagnostic assays, each laboratory should determine its own reference intervals for the diagnostic evaluation of patient results. Consider these values as a guideline only.

1. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Biology, Fourth Edition, Elsevier Saunders, St. Louis, MO; pp. 1253 (clinical significance), pp. 2315 (reference values).
2. Finn AL, Taylor WJ. Individualizing Drug Therapy, Practical Applications of Drug Monitoring. New York:Gross, Townsend, Frank, Inc., 1981: 87-108.

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.