

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

A. 510(k) Number:

k050419

B. Purpose for Submission:

New 510(k)

C. Analyte:

Vancomycin

D. Type of Test:

Quantitative Immunoassay

E. Applicant: Seradyn, Inc.

F. Proprietary and Established Names: Seradyn QMS® Vancomycin

G. Regulatory Information:

1. Regulation section: 21 CFR 862.3950 Vancomycin Test System
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 QMS® Vancomycin assay is intended for the quantitative determination of Vancomycin in human serum or plasma on the Hitachi 717 analyzer. The results obtained are used in the diagnosis and treatment of Vancomycin overdose and in monitoring levels of Vancomycin to ensure appropriate therapy.
3. Special condition for use statement(s):
N/A
4. Special instrument Requirements:
The device is for use on the Roche Hitachi 717 Analyzer.

I. Device Description:

The QMS® Vancomycin assay consists of separately packaged reagents (R1 and R2) and calibrators. R1 is the antibody reagent that contains Vancomycin mouse monoclonal antibody (mouse ascites) in a buffer as stabilizer and sodium azide as a preservative. R2 is Vancomycin micro-reagent that contains Vancomycin coated microparticles in buffer containing a surfactant and sodium azide as a preservative. Both reagents are supplied in liquid form. The calibrators that are included with the assay were previously cleared in k872644 as the Innofluor Vancomycin Calibrator Set. The calibrators consist of six levels of one ml in liquid frozen form.

The human serum used for the already cleared calibrators were tested by FDA approved methods and confirmed to be non-reactive for Hepatitis B surface Ag (HBsAg), HIV Type 1 and 2 Antibodies and Hepatitis C antibodies.

J. Substantial Equivalence Information:

1. Predicate device name(s):
TDX Vancomycin
2. Predicate K number(s):
k813218
3. Comparison with predicate:

Both devices are for measurement of the same analyte(s) in the same matrix, utilize the same test methodology and cutoff concentration. Both are for use on automated analyzers.

Similarities		
Item	Device	Predicate
Intended Use	The QMS® Vancomycin assay is intended for the quantitative determination of Vancomycin in human serum or plasma on the Hitachi 717 analyzer. The results obtained are used in the diagnosis and treatment of Vancomycin overdose and in monitoring levels of Vancomycin to ensure appropriate therapy.	TDx Vancomycin is a reagent system for the quantitative measurement of serum or plasma Vancomycin levels in the management of patients receiving Vancomycin therapy.
Analyte	Vancomycin	Vancomycin
Matrix	Serum or Plasma	Serum or Plasma
Storage	2-8 °C	2-8 °C

Differences		
Item	Device	Predicate
Methodology	Particle Enhanced Turbidimetric Immunoassay	Fluorescence Polarization (FPIA)
Assay Range	2.5 µg/L -100 µg/mL	2.0 µg/L -100 µg/mL

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

The sponsor referenced the following guidance document(s) in their submission:

NCCLS EP5-A: Evaluation of Precision Performance of Clinical Chemistry devices.

NCCLS EP6-P: Evaluation of the Linearity of Quantitative Analytical Methods.

NCCLS EP7-P: Interference Testing in Clinical Chemistry.

NCCLS EP9-A: Method Comparison and Bias Estimation Using Patient Samples

L. Test Principle:

The QMS Vancomycin assay is a homogeneous particle-enhanced turbidimetric immunoassay. The assay is based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the Vancomycin antibody reagent. The vancomycin-coated microparticle reagent (R2) is rapidly agglutinated in the presence of the anti-vancomycin antibody reagent (R1) and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically and is inversely proportional to the rate of agglutination of the particles. When a sample containing vancomycin is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained with maximum rate of agglutination at the lowest vancomycin concentration and the lowest agglutination rate at the highest vancomycin concentration.

M. Performance Characteristics (if/when applicable):1. Analytical performance:a. *Precision/Reproducibility:*

Precision was conducted and assessed according to NCCLS EP5-A. Two separate lots of the QMS Vancomycin reagents were run in duplicates for 20 non-consecutive days on the Hitachi 717 analyzers with QMS Vancomycin Calibrators and a commercially available control. Additionally, within run precision was conducted by re-running the samples again after 2 hours. The acceptance criterion was a total CV of less than 10%. The results for both lots are shown in the two tables below.

Precision for Lot 1			Within Run		Between Run		Between Day		Total	
	N	Mean	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Low Control	80	7.6 µg/mL	0.27	3.59	0.43	5.70	0.43	5.72	0.70	8.84
Mid Control	80	20.8 µg/mL	0.51	2.44	0.69	3.30	0.97	4.66	1.29	6.21
High Control	80	33.7 µg/mL	0.80	2.37	1.19	3.54	0.95	2.83	1.72	5.12

Precision for Lot 2			Within Run		Between Run		Between Day		Total	
	N	Mean	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Low Control	80	6.3 µg/mL	0.39	6.21	0.21	3.36	0.40	6.40	0.60	9.53
Mid Control	80	17.8 µg/mL	0.65	3.63	0.86	4.81	0.00	0.00	1.08	6.03
High Control	80	31.5 µg/mL	1.15	3.66	1.36	4.34	0.00	0.00	1.79	5.67

Commercially available control levels

Controls	Vancomycin (µg/mL)
Level 1	6.9 (5.5-8.30)
Level 2	22 (16-25)
Level 3	35 (28-42)

Accuracy by recovery was determined by spiking human serum that was negative for vancomycin with USP traceable vancomycin that covered the assay range. The samples were analyzed in triplicate with two lots of the QMS Vancomycin assay. Linear regression for lot 1 was $y=0.955x + 0.529$ ($R^2=0.9958$) and for lot 2 was $y=0.9632x + 1.153$ ($R^2=0.9965$).

b. Linearity/assay reportable range:

Linearity was conducted and assessed according to NCCLS EP6-A. The QMS Vancomycin Assay is designed to quantitate patient samples between 2.5 µg/mL to 100 µg/mL. Calibrator A (0 µg/mL) was used as the diluent and Calibrator F (100 µg/mL) was diluted to 75.0, 37.5, 17.5, 7.5 and 2.5 µg/mL midpoint samples. The samples were run in triplicate with two lots of the assay. Linear regression plots of USP Vancomycin against recovered vancomycin for Lot 1 was $y= 1.000x - 0.6113$ ($R^2= 0.9997$) and for Lot 2 was $y=1.0115x - 0.3769$ ($R^2=0.9998$).

c. *Traceability (controls, calibrators, or method):*

The QMS Vancomycin assay does not include vancomycin controls or calibrators. Calibrators were cleared under k872644. The controls used in with this assay are commercially available. The sponsor is the current owner and manufacturer of the Innofluor line and continues to manufacture the calibrators using the same validated procedures established at the time of clearance for k872644.

d. *Detection limit:*

The sensitivity, or lowest detectable dose (LDD), is defined by the sponsor as the lowest concentration of analyte detectable from zero with 95% confidence when performing the assay. Sensitivity was established by determining the average concentration of analyte present in 20 replicates of the negative Calibrator A with two lots of the QMS Vancomycin assay. The LDD was calculated using the following formula:

$$\text{LDD} = \frac{2 \times (\text{SD mAbs of Zero Cal})}{(\text{mAbs of Zero Cal} - \text{mAbs of 1}^{\text{st}} \text{ non-zero cal})} \times (\text{Conc of 1}^{\text{st}} \text{ non-zero Cal})$$

	Lot 1	Lot 2
N	20	20
Avg	1.01 µg/mL	0.22 µg/mL
SD	0.27 µg/mL	0.19 µg/mL
LDD	0.53 µg/mL	0.38 µg/mL

The average LDD was 0.46 µg/mL, which supports a claim of 0.55 µg/mL.

e. *Analytical specificity:*

Percent cross-reactivity was assessed according to the NCCLS EP7-A. The QMS Vancomycin assay utilizes a mouse derived (ascites) vancomycin monoclonal antibody directed against vancomycin. Specificity was conducted by determining cross-reactivity to the metabolites of vancomycin. In vivo, vancomycin degrades into its metabolite, CDP-I (crystalline degradation product-I). CDP-I has two forms, CDP-I major and CDP-I minor. The sponsor states difficulty in isolation of the major and minor atropisomers, isomers which arise by restricted rotation around a single bond, in sufficient

amounts for a cross reactivity study, so a combined cross reactivity study of CDP-I major: minor isomers was performed to obtain the total cross-reactivity of the metabolites. The metabolites at 100 µg/mL were spiked into serum with vancomycin at 25 µg/mL. The control sample was vancomycin in human serum with no metabolites. The control and spiked sample were assayed (n=5) using two lots of QMS Vancomycin assay in triplicate. Cross-reactivity was determined using the following equation:

$$= \frac{(\text{Conc. of vancomycin in spiked sample} - \text{conc. of vancomycin in control})}{\text{Conc. of Cross-reactant}} \times 100$$

If the numerator was less than a SD of the control, percent cross-reactivity was reported as not detectable. See the chart below.

Lot 1	N	Mean	SD	CV	Numerator	% Cross Reactivity
Control	5	25.30	0.90	3.56	-	-
100 µg/mL CDP-I	5	29.94	0.21	0.70	4.64	4.65
Lot 2	N	Mean	SD	CV	Numerator	% Cross Reactivity
Control	5	24.98	1.32	5.28	-	-
100 µg/mL CDP-I	5	29.95	0.86	2.87	4.61	4.61

The result show that CDP-I showed cross reactivity with the QMS Vancomycin assay that was less than 5%.

The cross-reactivity for Teicoplanin (a structurally similar compound) was conducted. Four concentrations of Teicoplanin was spiked into human serum containing 25 µg/mL vancomycin and tested with two lots of the QMS Vancomycin assay. The result of the cross-reactivity data is shown in the chart below and showed no cross-reactivity with the QMS Vancomycin assay.

Teicoplanin Concentration (µg/mL)	% Cross-Reactivity
100	0.68
50	0.29
25	0.20
10	0.03

Cross Reactivity of drugs that are commonly co-administered with vancomycin were tested in normal human serum. Cross-reactants were analyzed at 500 µg/mL in a vancomycin spiked serum pool at 25 µg/mL. Cross-reactant stock concentrations were either at 100x or 10x of the final concentration tested. Test samples were prepared

for each solvent system by combining 99 volumes of the stock analyte solution with 1 volume of 100x or 10x cross-reactant stock. Control aliquots were prepared for each solvent system by combining 99 volumes of the stock analyte solution with 1 volume of normal human whole blood. The test and control samples were run in triplicate and the cross-reactivities were calculated using the following formula.

$$\text{Percent Cross-Reactivity} = ((Da-Dt)/C) \times 100$$

Dt = average observed concentration of the control solution

Da = average of the observed concentration of the cross-reactant test solution

C = concentration at which the cross-reactant is tested.

The results of the cross-reactivity study for one lot is shown in the chart below.

Cross-reactant Drug	Avg.	SD	CV	Da-Dt	% Cross-reactivity
Acetaminophen	24.90	0.58	2.33	0.24	0.05
Amikacin	24.55	0.29	1.18	-0.12	-0.02
Amphotericin B	27.53	0.08	0.29	-0.37	-0.07
Ampicillin	24.83	0.20	0.82	0.40	0.08
Bendroflumethiazide	24.40	0.11	0.47	0.23	0.05
Caffeine	25.06	0.31	1.22	0.22	0.04
Carbenicillin	25.45	0.20	0.79	0.32	0.06
Cefamandole Nafate	23.83	0.16	0.67	-0.83	-0.17
Cefazolin	24.47	0.18	0.74	-0.19	-0.04
Cephalexin	24.56	0.42	1.69	-0.54	-0.11
Cephalosporin	24.83	0.28	1.12	-0.27	-0.05
Cephalothin	24.40	0.27	1.10	-0.70	-0.14
Chloramphenicol	24.80	0.37	1.49	0.14	0.03
Chlorothiazide	25.45	0.72	2.83	0.79	0.16
Clindamycin	27.64	0.21	0.76	0.43	0.09
Erythromycin	24.10	0.73	3.03	-0.56	-0.11
Ethacrynic Acid	24.63	0.30	1.22	-0.04	-0.01
Ethambutol	24.99	0.45	1.79	0.32	0.06
Fluorocytosine, 5-	24.38	0.92	3.76	-0.72	-0.14
Furosemide	24.89	0.25	0.99	0.23	0.05
Fusidic Acid	24.90	0.05	0.20	0.23	0.05
Gentamicin	27.22	0.88	3.24	0.04	0.01
Hydrochlorothiazide	24.95	0.20	0.80	0.29	0.06
Ibuprofen	24.31	0.26	1.08	-0.35	-0.07
Isoniazid	24.53	0.34	1.38	-0.24	-0.05
Kanamycin-A	25.08	0.87	3.48	0.23	0.05
Kanamycin-B	25.20	0.50	2.00	0.35	0.07
Lincomycin	25.14	0.55	2.19	0.48	.010
Methotrexate	27.13	0.07	0.27	-0.55	-0.11
Methyl Prednisolone	26.99	0.14	0.52	-0.22	-0.04
Nalidixic Acid	24.25	0.25	1.05	-0.85	-0.17
Naproxen	24.53	0.27	1.10	-0.14	-0.03
Neomycin Sulfate	25.46	0.10	0.40	0.62	0.12

Cross-reactant Drug	Avg.	SD	CV	Da-Dt	% Cross-reactivity
Niacin	24.84	0.60	2.43	0.17	0.03
Nitrofurantoin	24.81	0.28	1.15	0.15	0.03
Oxytetracycline	24.29	0.19	0.78	-0.37	-0.07
Penicillin G	24.60	0.13	0.54	-0.07	-0.01
Penicillin V	27.25	0.73	2.69	0.06	0.01
Phenacetin	24.50	0.44	1.79	-0.21	-0.04
Prednisolone	24.75	0.29	1.15	0.09	0.02
Prednisone	24.56	0.85	3.46	0.15	0.03
Rifampicin	25.04	0.47	1.88	0.37	0.07
Salicylic Acid	25.16	0.74	2.96	0.49	0.10
Sisomicin	27.52	0.37	1.33	0.34	0.07
Spectinomycin	24.42	0.33	1.34	-0.24	-0.05
Sulfadiazine	24.50	0.64	2.60	-0.16	-0.03
Sulfamethoxazole	24.68	0.23	0.93	0.02	0.00
Sulfisoxazole	24.56	0.74	3.01	-0.10	-0.02
Tetracycline	24.85	0.22	0.89	0.19	0.04
Tobramycin	24.05	0.28	1.18	-0.79	-0.16
Trimethoprim	24.45	0.41	1.69	-0.21	-0.04

*ND Data not obtained for sample; two replicates only

Interference testing was conducted in triplicates with two lots of the QMS Vancomycin assay according to the NCCLS protocol EP7-A. For the following interfering substances at the concentrations listed, the QMS Vancomycin assay showed less than a 10% error in detecting vancomycin.

Interfering Substances	Interference Concentration	N	Vancomycin (µg/mL)	Percent Recovery
Albumin	10 g/dL	3	24.92	93.64
Bilirubin	70 mg/dL	3	27.00	100.07
Cholesterol	500 mg/dL	3	25.97	97.58
IgG	6 g/dL	3	25.90	97.34
Hemoglobin	1150 mg/dL	3	21.18	91.64
HAMA Type-1	Normal human level	3	28.27	105.31
Hama-Type-2	Normal human level	3	28.55	103.91
Heparin	500 USP units/mL	3	26.46	99.44
Triglyceride	1000 mg/dL	3	9.41	92.62
RF	1100 IU/mL	3	6.70	93.23

f. Assay cut-off:
N/A

2. Comparison studies:*a. Method comparison with predicate device:*

Method comparison was conducted according to the NCCLS EP9-A to determine equivalence between the QMS Vancomycin and Abbott TDx Vancomycin assays. Clinical serum samples (146 samples for lot 1 and 148 samples for lot 2) were tested with the predicate and the device that ranged from 0.04 to 100 µg/mL vancomycin. The relationship between vancomycin concentrations derived using each device was evaluated using Passing-Bablok Linear regression. Mean values for the TDx reference methods were plotted against those for the QMS on Hitachi 717. The results for both lots are shown in the table below.

	Lot 1	Lot 2
N	146	148
Slope	1.03 (95% CI of 0.997 to 1.062)	1.05 (95% CI of 1.017 to 1.092)
Y Intercept	1.11 (95% CI of 0.58 to 1.55)	1.17 (95% CI of 0.56 to 1.73)
R²	0.970	0.964

b. Matrix comparison:

The sponsor demonstrated equivalence between serum and plasma by conducting the following studies: performance characteristics of the assay for serum and plasma studies, interferences when using different types of collection tubes and sample stability at 2 to 8 °C and -20 °C storage conditions.

Blood were drawn from six healthy volunteers (no vancomycin therapy) into plasma (4 types) and serum (3 types) tubes. Plasma (K2 and K3 EDTA, Lithium and Sodium Heparin) and serum (SST, plastic tube with clot activator and a plastic tube with no additive) samples were divided into two equal parts. Vancomycin was spiked at low (7.5 µg/mL) and high (30 µg/mL) concentrations into the plasma and serum pools and analyzed on a Hitachi 717 analyzer. The results are shown in the chart below and so now significant difference between the recovery of vancomycin in serum or plasma. The collection tube evaluated showed no adverse effects on the vancomycin recovery and supports the claim for both serum and plasma samples with the QMS Vancomycin assay.

Low Vancomycin (7.5 µg/ml)							
	K2 EDTA Tube	K3 EDTA Tube	Li Heparin Tube	Na Heparin Tube	Serum Separator Tube	Serum Tube with Clot Activator	Serum Tube (No Additive) Control
Rep 1	7.08	5.67	6.36	5.96	6.08	5.63	6.18
Rep 2	6.69	5.13	6.12	5.60	5.69	5.59	6.14
Rep 3	6.80	5.37	6.12	5.50	5.92	5.61	6.00
Average	6.86	5.39	6.20	5.69	5.90	5.61	6.11
Stdev	0.20	0.27	0.14	0.24	0.20	0.02	0.09
% CV	2.93	5.02	2.23	4.25	3.32	0.36	1.55
% Recovery	112.28	88.22	101.53	93.13	96.56	91.82	100.00

High Vancomycin (30 µg/ml)							
	K2 EDTA Tube	K3 EDTA Tube	Li Heparin Tube	Na Heparin Tube	Serum Separator Tube	Serum Tube with Clot Activator	Serum Tube (No Additive) Control
Rep 1	23.10	21.69	22.11	22.24	22.63	23.23	22.27
Rep 2	23.22	22.14	22.42	21.96	22.49	24.10	22.32
Rep 3	22.66	21.44	22.56	22.41	23.09	23.85	21.75
Average	22.99	21.76	22.36	22.20	22.74	23.73	22.11
Stdev	0.29	0.35	0.23	0.23	0.31	0.45	0.321
% CV	1.28	1.63	1.03	1.02	1.38	1.89	1.43
% Recovery	103.98	98.42	101.13	100.41	102.82	107.30	100.00

The samples from all tube types were divided into two portions and stored at 2-8 °C and -20 °C and retested at week one and week two to test anticoagulant interference. The results showed that there were no interferences with regard to recovery of vancomycin in serum or plasma for the 7 tube types tested. The results also showed that the samples are stable at both temperatures for at least 15 days.

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:

Therapeutic peak serum levels of 20- 40 µg/mL and trough levels of 5- 10 µg/mL have been reported for most strains of staphylococci and streptococci. However, therapeutic levels must be individually established based on patient differences and bacterial susceptibility. The risk of toxicity is appreciably increased by high concentration or prolonged therapy in patients with renal insufficiency. Toxic effects, such as ototoxicity and nephrotoxicity, have resulted when serum concentrations reach 80-100 µg/mL and are rarely seen when serum levels are maintained below 30 µg/mL.

Sponsor references literature for these expected values/reference ranges. Wilhelm MP, Vancomycin. Mayo Clinic Proc 1991; 66:1165-1170.

N. Conclusion:

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