

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

A. 510(k) Number:

k072036

B. Purpose for Submission:

New device

C. Measurand:

Vancomycin

D. Type of Test:

Quantitative Immunoassay

E. Applicant:

Biokit S.A.

F. Proprietary and Established Names:

ARCHTECT *i*Vancomycin Immunoassay

ARCHTECT *i*Vancomycin Calibrators (A-F)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LEH - Radio Immunoassay	Class II	21 CFR 862.3950 Vancomycin test system	Toxicology (91)
Product Code	Classification	Regulation Section	Panel
DLJ - Calibrator, drug specific	Class II	21 CFR 862.3200 Clinical toxicology calibrator	Toxicology (91)

H. Intended Use:

1. Intended use(s):

Refer to indications for use below.

2. Indication(s) for use:

Reagents

The ARCHTECT *i*Vancomycin assay is an *in vitro* chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of vancomycin in human serum or plasma on the ARCHTECT *i* System with *STAT* protocol capability. The ARCHTECT *i*Vancomycin assay is used in the diagnosis and treatment of vancomycin overdose and in monitoring levels of vancomycin to help ensure appropriate therapy.

Calibrators

The ARCHITECT *i*Vancomycin Calibrators are for the calibration of the ARCHITECT *i* System with *STAT* protocol capability when used for the quantitative determination of vancomycin in human serum or plasma.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

To be used with ARCHITECT *i* System with *STAT* protocol capability.

I. Device Description:

The device is supplied as ready-to-use, two-reagent kit. Microparticles containing reagent bottle 1 (6.6 mL) contains anti-vancomycin (mouse, monoclonal) coated goat anti-mouse (GAM) microparticles in TRIS buffer with protein (bovine) stabilizer and preservative: ProClin 300. Reagent bottle 2 (5.9 mL) contains Vancomycin acridinium-labeled conjugate in MES buffer with surfactant. Minimum concentration: 50 ng/mL. Preservative: ProClin 300.

J. Substantial Equivalence Information:

1. Predicate device name(s):

AxSYM Vancomycin II

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

k955851

3. Comparison with predicate:

Similarities

Characteristics	New Device (k072036)	AxSYM Vancomycin II (k955851)
Product Type	Immunoassay	Immunoassay
Intended Use (Reagent)	The ARCHITECT <i>i</i> Vancomycin assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of vancomycin in human serum or plasma on the ARCHITECT <i>i</i> System with <i>STAT</i> protocol capability. The ARCHITECT <i>i</i> Vancomycin assay is used in the diagnosis and treatment of vancomycin overdose and in monitoring levels of vancomycin to help ensure appropriate therapy.	The AxSYM Vancomycin II assay is a reagent system for the quantitative measurement of vancomycin, an antibiotic drug, in serum or plasma. The measurements obtained are used in monitoring levels of vancomycin to ensure appropriate therapy.
Intended Use (Calibrators)	The ARCHITECT Vancomycin Calibrators are for the calibration of the ARCHITECT <i>i</i> System with <i>STAT</i> protocol capability when used for the	The AxSYM Vancomycin II Standard Calibrators are for the standard calibration of the AxSYM System when used for the

Characteristics	New Device (k072036)	AxSYM Vancomycin II (k955851)
	quantitative determination of vancomycin in human serum or plasma	quantitative determination of vancomycin in human serum or plasma.
Where Used	Clinical Laboratories	Clinical Laboratories
Assay Protocol	Competitive assay	Competitive assay
Interpretation of Results	Standard Curve	Standard Curve
Measuring Range	0.24 µg/mL – 100.00 µg/mL	2.0 µg/mL – 100 µg/mL
Specimen Type	Serum or Plasma (collected in lithium heparin, potassium EDTA, sodium citrate, sodium fluoride/potassium oxalate and sodium heparin tubes)	Serum or Plasma (collected in sodium heparin, citrate, EDTA or oxalate collection tubes)
Standardization/Traceability	Internal Reference Calibrators are manufactured gravimetrically using USP Reference Standard Vancomycin Hydrochloride. The ARCHITECT <i>i</i> Vancomycin Calibrators are matched to the internal Reference Calibrators.	Abbott manufactures internal reference standards using Vancomycin Hydrochloride (USP Reference Standard). Vancomycin calibrators are manufactured gravimetrically and tested against these internal reference standards.
Calibrator Levels	6 levels	6 levels

Differences

Characteristics	New Device (k072036)	AxSYM Vancomycin II (k955851)
Platform	ARCHITECT <i>i</i> System	AxSYM System
Methodology	Chemiluminescent Microparticle Immunoassay (CMIA)	Fluorescence Polarization Immunoassay (FPIA)
Matrix	MES buffer and stabilizers	Dextrose buffer and stabilizers
Components	Microparticles - 1 bottle (6.6 mL) Anti-vancomycin (mouse, monoclonal) coated goat anti-mouse (GAM) microparticles in TRIS buffer with protein (bovine) stabilizer. Preservative: ProClin 300. Conjugate - 1 bottle (5.9 mL) Vancomycin acridinium-labeled	1 bottle (15.0mL) < 25% Vancomycin II Antiserum (Mouse, monoclonal) in buffer with protein stabilizers. Preservative: Sodium Azide (Reagent Bottle 1) 1 bottle (8.6 mL) Pretreatment Solution. Surfactant in TRIS buffer.

Characteristics	New Device (k072036)	AxSYM Vancomycin II (k955851)
	conjugate in MES buffer with surfactant. Minimum concentration: 50 ng/mL. Preservative: ProClin 300.	Preservative: Sodium Azide. (Reagent Bottle 2) 1 bottle (15.1 mL) < 0.01% Vancomycin II Fluorescein Tracer in buffer containing surfactant and stabilizers. Preservative: ProClin 300. (Reagent Bottle 3)
Matrix	MES buffer and stabilizers	Dextrose buffer and stabilizers

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

- CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Second 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

L. Test Principle:

The ARCHITECT *i*Vancomycin assay is a one-step *STAT* immunoassay for the quantitative measurement of vancomycin in human serum or plasma using CMIA technology, with flexible assay protocols, referred to as Chemiflex. Sample, anti-vancomycin coated paramagnetic microparticles, and vancomycin acridinium-labeled conjugate are combined to create a reaction mixture. The anti-vancomycin coated microparticles bind to vancomycin present in the sample and to the vancomycin acridinium-labeled conjugate. After washing, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). An indirect relationship exists between the amount of vancomycin in the sample and the RLUs detected by the ARCHITECT *i* System optics.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Following CLSI EP5-A2, the sponsor evaluated the precision using two lots of reagents and three levels of Multiconstituent Controls (MCC Level 1, MCC Level 2, MCC Level 3) and three serum panels prepared by adding vancomycin into a pool of human sera to obtain desired concentration of vancomycin. Precision tests were run on two ARCHITECT *i* systems. Studies were carried out in duplicates of two runs per day over 20 days (total of 80 data points). The sponsor's acceptance was designed to maintain $\leq 10\%$ total CV. The results are tabulated below.

Sample	Instrument/ Reagent Lot	n	Mean (µg/mL)	Within Run		Between Run		Total	
				SD	%CV	SD	%CV	SD	%CV
Level 1	1/1	80	6.9	0.16	2.3	0.09	1.3	0.22	3.1
	2/2	80	6.1	0.11	1.6	0.11	1.6	0.35	5.0
Level 2	1/1	80	20.3	0.37	1.9	0.36	1.9	0.66	3.4
	2/2	80	18.6	0.39	2.0	0.23	1.2	0.95	4.9
Level 3	1/1	80	35.9	0.66	2.0	0.86	2.6	1.15	3.5
	2/2	80	33.1	0.70	2.1	0.54	1.6	1.68	5.1
Panel 1	1/1	80	6.5	0.18	2.8	0.06	0.9	0.24	3.8
	2/2	80	5.7	0.14	2.3	0.05	0.9	0.27	4.4
Panel 2	1/1	80	37.3	0.96	2.9	0.70	2.1	1.38	4.2
	22	80	33.8	0.87	2.7	0.14	0.4	1.60	4.9
Panel 3	1/1	80	67.4	1.89	2.7	2.43	3.4	4.40	6.2
	2/2	80	70.1	2.11	3.0	1.38	2.0	3.16	4.5

b. Linearity/assay reportable range:

The sponsor conducted studies on the T60 instrument to evaluate the dilution recovery of the ARCHITECT *i*Vancomycin assay using CLSI Document EP6-A as a guideline. The sponsor used five pooled frozen serum samples (Vancomycin values: 40-86 µg/mL) and a calibrator (Calibrator F: 105 µg/mL) diluted manually with both ARCHITECT *i*Vancomycin Calibrator A and ARCHITECT Multi-assay manual diluent. Each of the five samples was diluted to maintain 11 test concentration levels separately using Calibrator A and multi-assay diluent. Testing was done using one reagent lot and running duplicates of each diluent level. The results demonstrated at each dilution level for all five samples, and for both Calibrator A and ARCHITECT Multi-assay manual diluent, diluted sample values recovered from 98% to 117%. Based on the recovery data and the limit of detection described below, the sponsor established the assay reportable range for ARCHITECT *i*Vancomycin assay as 0.24 µg/mL – 100.00 µg/mL.

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

The sponsor provides calibrator materials and recommends using commercially available control materials for quality control procedure. The sponsor provided the protocols for preparation and value assignment for calibrators. The Internal Standard Calibrators are manufactured gravimetrically using purified synthetic Vancomycin from the US Pharmacopeia (USP) Reference Standard Vancomycin (Ref. 1709007). The ARCHITECT *i*Vancomycin Calibrators are matched to the Internal Standard Calibrators, which consists of calibrator buffer (MES, Dextrose and ProClin 300), Vancomycin and stabilizer.

The sponsor conducted all stability studies including accelerated stability studies for long-term storage. The sponsor's studies demonstrated the following limits: open-vial stability of 4 months; long-term storage of 8 months; and on-board stability of 30 days. The assay labeling indicates that when the reagent is stored and handled as directed, the reagents are stable until expiration date on the bottle.

d. Limit of Detection:

To demonstrate the lower limit of the assay range, the sponsor performed the limit of detection (LOD) and limit of blank (LOB) tests using CLSI document EP17-A “Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline” The sponsor used 2 instruments, 2 lots of reagents and 2 lots of calibrators for testing on a panel of 4 samples with low vancomycin concentrations and a sample (NHS) with 0 µg/mL. The samples with vancomycin were prepared by diluting low vancomycin serum sample (11.6µg/mL) with NHS sample to achieve concentrations of 1.0, 1.5, 2 and 2.5 µg/mL. Three runs were performed for each reagent lot. Each run consisted of 20 replicates of NHS (0 µg/mL) and 5 replicates of each panel member for a total of 60 replicates of NHS and 15 replicates of each panel member were analyzed. Based on the 95th percentile calculation described in the CLSI EP17-A, LOD was determined using the algorithm, $LoD = LoB + [1.645 / (1 - 1 / 4 \times df)] \sigma_S$. The mean LOB and LOD were determined as 0.12 µg/mL and 0.24 µg/mL, respectively.

e. Analytical specificity:

Following instructions in CLSI document EP7-A2, the sponsor evaluated the effect of known endogenous interferents on Architect i System using one lot of reagents. The interferents and the test range included triglycerides (2500 mg/dL), hemoglobin (500 mg/dL), low protein (3 g/dL), high protein (10 g/dL), HAMA (1000 ng/mL), rheumatoid factor 500 IU/mL, and bilirubin (20 mg/dL). Five human serum samples with Vancomycin concentrations targeted at 5, 10, 25, 40 and 80 µg/mL were used to prepare the interfering panel. These human serum samples were spiked with the interferent for the test sample. An equal volume of interferent diluent was spiked into the samples to prepare the control sample. The results are listed in the table below. The sponsor claimed no interference with recovery $\pm 15\%$ for the above interferents and up to the concentrations tested.

Interferent	Sample	Expected (Control Vanco Conc. µg/mL)	Observed (Test Vanco Conc. µg/mL)	% Recovery	Mean % Recovery
Hemoglobin 500 mg/dL	1	4.5	4.6	101.5	104.4
	2	8.9	9.4	104.6	
	3	22.1	22.8	102.8	
	4	39.8	42.1	105.9	
	5	76.6	82.0	107.1	
Bilirubin 20 mg/dL	1	4.3	4.3	100.0	101.6
	2	8.7	8.7	100.2	
	3	21.4	21.5	100.7	
	4	39.1	39.9	102.1	
	5	73.1	76.9	105.1	
Triglycerides 2500 mg/dL	1	4.5	4.6	101.7	99.9
	2	9.1	9.0	98.7	
	3	23.1	23.1	99.9	
	4	42.3	41.9	99.1	

Interferent	Sample	Expected (Control Vanco Conc. µg/mL)	Observed (Test Vanco Conc. µg/mL)	% Recovery	Mean % Recovery
	5	83.7	83.6	99.9	
High Protein 10 g/dL (100g/L)*	2	8.7	8.7	100.0	98.9
	6	13.7	13.3	97.3	
	3	21.9	22.4	101.9	
	4	40.5	39.1	96.5	
	5	77.9	76.9	98.7	
Low Protein 3 g/dL (30 g/L)*	2	8.7	8.4	96.9	106.6
	6	13.7	14.3	104.2	
	3	21.9	23.6	107.5	
	4	40.5	44.5	110.0	
	5	77.9	89.2	114.5	
RF 500 IU/mL	1	4.3	4.3	99.0	99.3
	2	8.6	8.4	98.2	
	3	21.0	21.5	102.1	
	4	38.7	38.7	99.8	
	5	75.3	73.3	97.3	
HAMA 1000 ng/mL	1	4.6	4.6	101.1	99.8
	2	9.0	8.9	99.0	
	3	22.2	22.5	101.1	
	4	40.9	40.4	98.7	
	5	76.7	76.0	99.2	

** Sample 1 when diluted had an initial concentration of Vancomycin less than 2µg/mL, less than the designed LoD of the assay. An additional sample 6 target at 15µg/mL was added to the data set.*

Following CLSI EP7-A2 guidelines, the sponsor conducted a study to evaluate the potential cross-reactivity of the ARCHITECT *i*Vancomycin assay when tested with structurally similar compounds. A pool of sera containing essentially no residual vancomycin was split into 3 different parts. Two parts were spiked with vancomycin to reach target concentrations of 7 and 35 µg/mL and the third part was not spiked with vancomycin. Therapeutic interferents listed in the table below were dissolved at concentrations 20 times greater than the desired testing concentrations. Therapeutic concentrates were spiked into the samples above to prepare the test sample and an equal volume of the interferent diluent was spiked to the samples to prepare the control sample. Each sample was tested in three replicates. Based on these studies, the sponsor demonstrated when there is no vancomycin present, all tested therapeutics have no potential cross-reactivity above the LOD. In the presence of vancomycin, no influence from tested therapeutics was observed based on the criteria, change in vancomycin measured should be less than the designed LOD of the assay and the mean % Recovery of Vancomycin is 100 +/- 10%.

Potential interfering therapeutics with ARCHITECT *i*Vancomycin assay tested at a concentration of 500 µg/mL (exception: CDP-1 was tested at 50 µg/mL and Methotrexate, tested at 227µg/mL).

Acetaminophen	Chlorothiazide	Isoniazid	Rifampin
Amikacin	Ciprofloxacin	Kanamycin B	Salicylic acid
Amphotericin B	Erythromycin	Methotrexate	Spectinomycin
Ampicillin	Ethambutol	Methylprednisolone	Streptomycin
Caffeine	5-fluorocytosine	Naproxen	Sulfadiazine
CDP-1	Furosemide	Neomycin	Sulfamethixazole
Cephalexin	Gentamicin	Nitrofurantoin	Tetracycline
Cephalosporin C	Heparin	Penicillin G	Ticarcillin
Cephalothin	Hydrochlorothiazide	Penicillin V	Tobramycin
Clindamycin	Ibuprofen	Prednisolone	Trimethoprim
Chloramphenicol			

f. Assay cut-off:

Not Applicable.

2. Comparison studies:

a. Method comparison with predicate device:

To demonstrate the substantial equivalence to the predicate device, the sponsor conducted a method comparison study with samples using ARCHITECT *i*Vancomycin Reagent on ARCHITECT *i* System and Abbott AxSYM Vancomycin II. Using a total of 206 frozen serum samples (range: 0-100 µg/mL) (86 samples were spiked to achieve concentrations of 40-100 µg/mL, 120 natural samples ranged from 0-40 µg/mL), the study was performed over 4 days, generating calibration curves on each testing day. Samples that fell within the measuring range for each assay were used for calculations. A total of 192 samples were used for calculations. The analysis of data using Passing & Bablok and least squares method produced regression equations $y = 0.9249x + 0.0502$ and $y = 0.9016x + 0.7905$. The following table demonstrates the correlation between the two methods. Fourteen samples were not included in the analysis because they were below the detection limit.

ARCHITECT vs. AxSYM		95% CI	
Correlation Coefficient (Pearson)	0.9964	0.9952	0.9973
Passing & Bablok slope	0.9249	0.9123	0.9381
Passing & Bablok intercept	0.0502	-0.1172	0.2509
Linear (least square) Regression slope	0.9016	0.8906	0.9126
Linear Regression (least square) intercept	0.7905	0.2915	1.2895
Concentration range AxSYM (µg/mL)	2.1-94.3		
Concentration range ARCHITECT (µg/mL)	1.4-83.5		
N	192		

A bias analysis of ARCHITECT *i*Vancomycin vs AxSYM Vancomycin II performed on the same 192 specimens (2.1 to 94.3 µg/ml) exhibited an average bias of -7.29% (95% CI: -23.40 to 8.82%). Within the typical therapeutic range of vancomycin therapy (5-40 µg/mL), the average bias was -4.41% (95% CI: -19.51 to 10.70%).

b. Matrix comparison:

The sponsor conducted matrix comparison studies using 20 matched serum and plasma samples prepared with five different anticoagulants (K-EDTA, Na-Citrate, Na- Fluoride/K-Oxalate, Na-Heparin and Li-Heparin) used for plasma. Serum tubes without anticoagulants were used as the control. To evaluate the anticoagulant effect along the assay measuring range, each of the 20 sets of serum/plasma tubes were spiked with vancomycin to obtain 10 different spiking concentrations. (5, 7.5, 10, 15, 20, 30, 40, 60, 70 and 80 µg/mL). The samples were analyzed in triplicate with one lot of ARCHITECT *i*Vancomycin reagents on the ARCHITECT *i* System. Based on the sponsor's acceptance criteria of mean % recovery value within 100 ± 10% of the serum value, data tabulated below supports the plasma can be used to determine the vancomycin level in blood.

Sample type	No.	Mean % recovery vs. Serum
Serum with no additive	20	Control
K-EDTA	20	100.6
Na-Citrate	20	106.9
Na-Fluoride/K-Oxalate	20	101.0
Na-Heparin	20	101.4
Li-Heparin	20	101.2

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):

4. Clinical cut-off:

Not Applicable.

5. Expected values/Reference range*:

In the labeling, the sponsor states, as supported by literature, therapeutic peak serum levels of 20 to 40 µg/mL and trough levels of 5 to 10 µg/mL have been reported to be effective for most strains of staphylococci and streptococci. The sponsor recommends in the labeling that users establish the therapeutic levels of vancomycin based on patient differences and bacterial susceptibility. For diagnostic purposes, the test findings should always be assessed in conjunction with the patient's medical history, clinical examinations, and other findings.

- * 1. Wilhelm MP. Vancomycin. Mayo Clin Proc 1991;66:1165–70.
- 2. Cook FV, Farrar WE Jr. Vancomycin revisited. Ann Intern Med 1978;88(6):813–8.

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.