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

A. 510(k) Number:
k123947

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:
ARCHITECT *i*Vancomycin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LEH	Class II	21 CFR 862.3950 Vancomycin test system	Toxicology (91)

H. Intended Use:

1. Intended use(s):
   Refer to indications for use below.
2. Indication(s) for use:

   Reagents
   The ARCHITECT *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* System with *STAT* protocol capability. The ARCHITECT *i*Vancomycin assay is used in the diagnosis and treatment of vancomycin overdose and in monitoring levels of vancomycin to help ensure appropriate therapy.
3. Special conditions for use statement(s):
   For in vitro diagnostic use only
4. Special instrument requirements:
   ARCHITECT *i*2000SR System with *STAT* protocol capability.

I. Device Description:

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.

Each *i*Vancomycin Reagent kit contains 1 bottle of each component of Conjugate and Microparticles.

- Conjugate – 1 bottle (5.9 mL) Vancomycin acridinium-labeled conjugate in MES buffer with surfactant. Minimum concentration: 50 ng/mL. Preservative: ProClin 300.
- 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.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   ARCHTECT *i*Vancomycin
2. Predicate 510(k) number(s):
   k072036
3. Comparison with predicate:

Similarities		
Characteristics	**Candidate Device (k123947)**	**Predicate Device (k072036)**
Device Name	ARCHITECT *i*Vancomycin	Same
Indications for Use (Reagent)	The ARCHITECT *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* System with STAT protocol capability. The ARCHITECT *i*Vancomycin assay is used in the diagnosis and treatment of vancomycin overdose and in monitoring levels of Vancomycin to help ensure appropriate therapy.	Same
Platform	ARCHITECT *i* System	Same
Methodology	Chemiluminescent immunoassay	Same
Assay Protocol	Competitive assay	Same
Calibrators	6 Level calibrators with Model # LN 1P30-01	Same
Components of 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	Same

Specimen type	Serum or Plasma (collected in dipotassium EDTA, sodium citrate, sodium fluoride/potassium oxalate, lithium heparin, and sodium heparin tubes)	Same

Differences		
Characteristics	**Candidate Device (k123947)**	**Predicate Device (k072036)**
Model number	1P30-28	1P30-25
Limit of Blank (LoB) Limit of Detection (LoD) Limit of Quantitation (LoQ)	LoB: 0.27 µg/mL LoD: 0.42 µg/mL LoQ: 2.50 µg/mL	LoB: 0.12 µg/mL LoD: 0.24 µg/mL LoQ: not determined
Measurement Range	3.0 µg/mL – 50.0 µg/mL	0.24 µg/mL – 100.0 µg/mL
Components of Conjugate	1 Bottle (5.9 mL) Vancomycin acridinium-labeled conjugate in MES buffer with surfactant (without Geropon). Minimum concentration: 50 ng/mL. Preservative: ProClin 300.	1 Bottle (5.9 mL) Vancomycin acridinium-labeled conjugate in MES buffer with surfactants (containing Geropon 0.75%). Minimum concentration: 50 ng/mL. Preservative: ProClin 300.

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

- CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline- 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
- CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples: Approved Guideline- Second Edition

L. Test Principle:

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 precision using two lots of reagents, three levels of Multi-Constituent Controls (MCC Level 1, MCC Level 2, MCC Level 3) and four serum panels prepared by adding vancomycin into a pool of human sera to obtain desired concentration of vancomycin. Precision tests were carried out on two ARCHITECT *i*2000SR systems with three replicates per run, two runs per day over 20 days (total of 120 data points per instrument per reagent lot). The results are tabulated below.

Sample	instrument	Reagent lot	N	Mean	Within run		Total	
				(µg/mL)	SD	%CV	SD	%CV
MCC Level 1	1	1	120	6.77	0.17	2.5	0.19	2.8
	1	2	120	6.75	0.20	3.0	0.27	4.1
	2	1	120	6.70	0.20	2.9	0.21	3.1
	2	2	120	6.62	0.17	2.6	0.24	3.7
MCC Level 2	1	1	120	23.38	0.61	2.6	0.66	2.8
	1	2	120	22.82	0.63	2.7	0.91	4.0
	2	1	120	23.17	0.70	3.0	0.79	3.4
	2	2	120	22.32	0.52	2.3	0.75	3.4
MCC Level 3	1	1	120	39.61	0.85	2.1	1.10	2.8
	1	2	120	38.30	0.85	2.2	1.33	3.5
	2	1	120	39.33	0.84	2.1	1.00	2.5
	2	2	120	37.94	0.97	2.6	1.22	3.2
Panel 1	1	1	120	3.27	0.10	2.9	0.13	4.0
	1	2	120	3.31	0.12	3.5	0.15	4.6
	2	1	120	3.23	0.11	3.3	0.12	3.8
	2	2	120	3.26	0.11	3.4	0.16	4.9
Panel 2	1	1	120	4.97	0.17	3.4	0.20	4.0
	1	2	120	4.95	0.14	2.8	0.24	4.8
	2	1	120	4.92	0.14	2.8	0.16	3.3
	2	2	120	4.89	0.12	2.5	0.22	4.4
Panel 3	1	1	120	10.00	0.26	2.6	0.31	3.1
	1	2	120	9.80	0.25	2.5	0.39	4.0
	2	1	120	9.89	0.23	2.3	0.28	2.8
	2	2	120	9.63	0.22	2.3	0.34	3.6
Panel 4	1	1	120	45.18	1.11	2.5	1.22	2.7
	1	2	120	43.55	1.17	2.7	1.63	3.8
	2	1	120	45.07	1.03	2.3	1.27	2.8
	2	2	120	43.37	1.13	2.6	1.55	3.6

The overall precision performance is summarized below:

Sample	N	Overall Mean (µg/mL)	Overall SD	Overall %CV
MCC Level 1	480	6.71	0.24	3.5%
MCC Level 2	480	22.92	0.87	3.8%
MCC Level 3	480	38.80	1.35	3.5%
Panel 1	480	3.27	0.14	4.4%
Panel 2	480	4.93	0.21	4.2%
Panel 3	480	9.83	0.36	3.6%
Panel 4	480	44.29	1.64	3.7%

b. Linearity/assay reportable range:

The sponsor conducted a recovery study using eight levels of spiked samples covering the measurement range. Five samples per spiked level were prepared by adding reference standard vancomycin into a pool of human sera to obtain desired concentration of vancomycin and tested in replicates of 3 using one lot of reagents on one ARCHITECT *i*2000SR instrument. The overall % recovery for each spiked level was determined and evaluated for acceptance. The results are tabulated below. Additional recovery information at low levels is shown in the LoQ study (see below).

Spiked level (µg/mL)	Overall %recovery
3.2	86.4%
5.0	98.0%
7.5	102.8%
10	104.4%
15	105.4%
20	104.4%
30	101.5%
45	99.1%

The sponsor also conducted studies on one *i*2000SR instrument to support linearity by preparing three high pools, which were diluted with normal human serum to ranging from levels below 3 to above 50 µg/mL vancomycin. Each set of samples from the same dilution series was tested within a run in 4 replicates at each dilution level. The results supported a linear range of 3.0 µg/mL – 50.0 µg/mL for ARCHITECT *i*Vancomycin assay.

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

Calibrators were previously cleared under k072036. See k072036 for more information.

d. Detection Limits:

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Detection (LoQ) were determined based on CLSI guideline EP17-A as described below:

Limit of Blank (LoB):

A total of 160 replicates of 4 zero-level Normal Human Serum (NHS) samples were tested over 3 days in 5 runs using 2 reagent lots and 2 instruments. The results were ordered according to their values and the 95th percentile of the zero-level samples concentration level was deemed as LoB level. The sponsor claimed the LoB = 0.27 µg/mL.

Limit of Detection (LoD):
A panel of 8 low level samples was tested over 3 days in 5 runs using 2 reagent lots and 2 instruments. The low level samples were prepared by diluting low vancomycin serum sample (23.88 µg/mL) with NHS sample to achieve concentrations of 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5 µg/mL. LOD was determined using the algorithm: LoD = LoB + {1.645 / [1-1/(4 x df)]}x SD, where SD is the standard deviation for the lowest level sample that has ≥95% replicate results greater than LoB level. The sponsor claimed the LoD = 0.42 µg/mL.

Limit of Detection (LoQ):
Observed total error was calculated for the 8 low level samples (described in LoD study) as Total Error = %Bias + 2x%CV. The LoQ study results supports the sponsor's claimed lower limit of 3.0 µg/mL. Results of precision and bias estimations for samples at the claimed lower limit are shown below:

Target	Mean	% bias	% CV	% total error
3.00	3.05	1.5	6.8	15.1

e. Analytical specificity:

Following CLSI document EP7-A2, the sponsor evaluated the effect of known endogenous interferents on Architect *i*2000SR System using one lot of reagents. The interferents and the test range included triglycerides (2500 mg/dL), hemoglobin (500 mg/dL), protein (12 g/dL), and bilirubin (20 mg/dL). Four human serum samples with Vancomycin concentrations targeted at 5, 10, 25, and 40 µg/mL were used to prepare the interfering panel. These human serum samples were spiked with the interferent for the test sample. Three normal human serum samples were spiked with vancomycin at target concentrations 5, 10, 20, 40 and 45 µg/mL and were used to prepare interfering panels for RF (500 IU/mL) and HAMA (1000 ng/mL). An equal volume of interferent diluent was spiked into the samples to prepare the control sample. The results demonstrated no interference from potential interferents tested at the concentrations shown below based on the Sponsor's criteria of % recovery within 100% ± 10%.

Bilirubin up to 20 mg/dL
Hemoglobin up to 400 mg/dL
Triglycerides up to 2500 mg/dL
Protein up to 12 g/dL
HAMA up to 1000 ng/mL
Rheumatoid Factor up to 500 IU/mL

Potential interfering therapeutics were tested with ARCHITECT *i*Vancomycin assay for interference at a concentration of 500 µg/mL (exceptions: crystalline degradation product-1 (CDP-1) tested at 50 µg/mL, Methotrexate tested at 227µg/mL). Four human serum samples with Vancomycin concentrations targeted at 0, 7, 35, and 45 µg/mL were prepared with and without the potential cross-reactants and tested in replicates of 25 in a single run.

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	Nirtrofurantoin	Tetracycline
Cefotaxime	Heparin	Penicillin G	Ticarcillin
Cephalothin	Hydroclorothiazide	Penicillin V	Tobramycin
Clindamycin	Ibuprofen	Prednisolone	Trimethoprim
Chloramphenicol			

The drugs listed above (except for CDP-1 and isoniazid) at the concentrations tested demonstrated no interference using the Sponsor's criteria of %recovery within 100% ± 10%:

- CDP-1 at ≥5 µg/mL interferes with samples containing vancomycin in the measurement range;
- Isoniazid at >300 µg/mL interferes with samples containing vancomycin in the measurement range.

f. Assay cut-off:

Not Applicable.

2. Comparison studies:

a. Method comparison with predicate device:

To further demonstrate substantial equivalence to the predicate device, the sponsor conducted a method comparison study with 120 neat human serum samples over 3 days using two lots of the candidate ARCHITECT *i*Vancomycin Reagent, and one lot of predicate ARCHITECT *i*Vancomycin Reagent (k072036). 107 samples that were within the measuring range for each assay were used for calculations. Passing & Bablok regression and bias analyses were provided. Results are summarized below:

Candidate ARCHITECT iVancomycin (Y) vs. Predicate ARCHITECT iVancomycin (X)

Linear regression: Y=1.04X -0.23; r=0.99, N=107. Samples range from 7.3 to 47.5 µg/mL.

A bias analysis of candidate ARCHITECT *i*Vancomycin vs. predicate ARCHITECT *i*Vancomycin performed on the 107 samples exhibited an average bias of 3.0% (95% CI: 2.1 to 4.0%).

b. Matrix comparison:

The sponsor conducted matrix comparison studies and concluded that serum and five kinds of plasma tubes (K_2-EDTA, Na-Citrate, Na-Fluoride/K-Oxalate, Li-Heparin and Na-Heparin) as acceptable specimen collection tubes in their PI. Recoveries for each tube type were compared with serum tubes at concentrations across the assay ranging from 3.2 to 45 µg/mL. Recoveries at each level were within the Sponsor's criterion of 100% ±10% recovery for each tube type.

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:
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.