

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

A. 510(k) Number:

k102699

B. Purpose for Submission:

New Device

C. Measurand:

Gentamicin

D. Type of Test:

Quantitative, chemiluminescent microparticle immunoassay

E. Applicant:

Abbott Laboratories Diagnostics Division

F. Proprietary and Established Names:

ARCHITECT *i*Gentamicin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
Enzyme Immunoassay, Gentamicin (LCD)	Class II	21 CFR 862.3450	Toxicology (91)
Calibrators, Drug Specific (DLJ)	Class II	21 CFR 862.3200	Toxicology (91)

H. Intended Use:

1. Intended use(s):

Reagents:

The ARCHITECT *i*Gentamicin assay is an *in vitro* chemiluminescent

microparticle immunoassay (CMIA) for the quantitative determination of gentamicin, an antibiotic drug, in human serum or plasma on the ARCHITECT *i* System with *STAT* protocol capability. The measurements obtained are used in the diagnosis and treatment of gentamicin overdose and in monitoring levels of gentamicin to help ensure appropriate therapy.

Calibrators:

The ARCHITECT *i*Gentamicin Calibrators are for the calibration of the ARCHITECT *i* System with *STAT* protocol capability when used for the quantitative determination of gentamicin, an antibiotic drug, in human serum or plasma.

2. Indication(s) for use:

See intended use, above.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

Evaluations represented in the 510(k) were performed on the ARCHITECT *i*2000_{sr} with *STAT* protocol capability.

I. Device Description:

The *in vitro* diagnostic device consists of the following reagents:

Microparticles (1bottle with 7.11mL) - Anti-gentamicin (mouse, monoclonal) coated microparticles in TRIS buffer with protein (bovine) stabilizers and preservatives (ProClin 950 and sodium azide). Conjugate (1 bottle with 11.75 mL) - A conjugate solution containing gentamicin acridinium-labeled conjugate in MES buffer and ProClin 300 as a preservative.

ARCHITECT *i*Multi-Assay Manual Diluent containing a phosphate buffered saline solution and an antimicrobial agent as a preservative. ARCHITECT *i*Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide. ARCHITECT *i*Trigger Solution containing 0.35 N sodium hydroxide. ARCHITECT *i*Wash Buffer containing phosphate buffered saline solution and antimicrobial agents to preserve wash buffer solution.

Calibrator:

The ARCHITECT *i*Gentamicin Calibrators set contains a six level set (0.00, 0.30,

1.50, 5.00, 8.00, 10.00 µg/mL or Calibrators A to F) of a single analyte (gentamicin) calibrators in recalcified human plasma and contains ProClin 950 and sodium azide as preservatives. The human plasma used in the calibrators were tested and found to be nonreactive for HBsAg, HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, and anti-HCV Testing was performed by a FDA licensed method.

J. Substantial Equivalence Information:

1. Predicate device name(s): AxSYM Gentamicin Assay
2. Predicate 510(k) number(s): k935376
3. Comparison with predicate:

Similarities:

Reagents		
Characteristics	Device	Predicate
Intended Use	Same	a reagent system for the quantitative measurement of gentamicin, an antibiotic drug, in serum or plasma.
Product Type	Immunoassay	Same
Methodology	Chemiluminescent Microparticle Immunoassay (CMIA)	Fluorescence Polarization Immunoassay (FPIA)
Where Used	Clinical Laboratories	Same
Assay Protocol	Competitive	Same
Calibration Curve Type	6-point	Same
Measuring Interval	0.3 µg/mL – 10.0 µg/mL	Same
Specimen Type	Serum or Plasma	Same
Instrumentation	ARCHITECT <i>i</i> 2000 _{SR}	AxSYM
Calibrator Materials		
Intended Use	Same	for the calibration of the the quantitative measurement of gentamicin, an antibiotic drug, in serum or plasma.
Calibrator Levels	6 levels	Same

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

1. EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

2. EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
3. EP7-A2: Interference Testing in Clinical Testing; Approved Guideline – Second Edition
4. EP9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition
5. EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

The ARCHITECT *i*Gentamicin assay is an in vitro chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of gentamicin in human serum or plasma. Anti-gentamicin coated paramagnetic microparticles, and gentamicin acridinium-labeled conjugate are combined to create a reaction mixture. The anti-gentamicin coated microparticles bind to the gentamicin present in the sample and to the 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 gentamicin in the sample and the RLUs detected by the ARCHITECT *i*System optics.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

Performance was validated on the ARCHITECT *i*2000_{SR} with STAT protocol capability.

a. Precision/Reproducibility:

Precision was evaluated on two ARCHITECT *i*2000_{SR} instruments using two lots of reagent, one lot of calibrators, and one lot of commercially available controls. Serum panels were prepared by spiking USP gentamicin gravimetrically into human serum resulting in the following gentamicin concentrations: ≤ 0.3 $\mu\text{g/mL}$, 1.0 $\mu\text{g/mL}$, 4.0 $\mu\text{g/mL}$, and ≥ 8.5 $\mu\text{g/mL}$. A single calibration per reagent was performed in replicates of two (stored for the duration of the study) and controls and serum panels were run in three replicates, twice daily for 20 days. Results are shown below.

Sample	Instrument	Reagent Lot	N	Mean (µg/mL)	Within Run		Total	
					SD	%CV	SD	%CV
Control Level 1	1	1	120	1.2	0.03	2.3	0.03	2.4
		2	120	1.2	0.03	2.3	0.03	2.4
	2	1	120	1.3	0.03	2.0	0.03	2.3
		2	120	1.3	0.03	2.2	0.03	2.4
Control Level 2	1	1	120	3.7	0.08	2.3	0.10	2.7
		2	120	3.7	0.11	2.9	0.12	3.2
	2	1	120	3.8	0.12	3.1	0.12	3.1
		2	120	3.9	0.11	2.9	0.12	3.1
Control Level 3	1	1	120	6.5	0.20	3.1	0.23	3.5
		2	120	6.8	0.28	4.1	0.36	5.3
	2	1	120	6.9	0.25	3.7	0.29	4.2
		2	120	6.8	0.26	3.8	0.27	4.0
Panel 1	1	1	120	0.2	0.01	2.7	0.01	4.3
		2	120	0.2	0.01	2.7	0.01	4.4
	2	1	120	0.3	0.01	2.8	0.01	3.1
		2	120	0.3	0.01	2.8	0.01	3.1
Panel 2	1	1	120	1.0	0.03	2.8	0.03	3.5
		2	120	1.0	0.02	2.0	0.03	3.2
	2	1	120	1.0	0.02	1.9	0.02	2.0
		2	120	1.0	0.02	2.5	0.03	2.8
Panel 3	1	1	120	3.6	0.10	2.9	0.14	3.9
		2	120	3.6	0.13	3.6	0.14	3.9
	2	1	120	3.8	0.10	2.6	0.11	2.9
		2	120	3.7	0.10	2.6	0.11	3.1
Panel 4	1	1	120	8.2	0.31	3.7	0.35	4.3
		2	120	8.4	0.37	4.4	0.44	5.2
	2	1	120	8.6	0.31	3.6	0.33	3.8
		2	120	8.3	0.38	4.5	0.42	5.0

b. *Linearity/assay reportable range:*

The claimed measurement range of the ARCHITECT *i*Gentamicin assay is 0.3µg/mL to 10.0 µg/mL

To demonstrate linearity across the assay range, three sets of 11 samples with expected gentamicin concentrations ranging between 0 µg/mL and 11.21 µg/mL were prepared. The samples were tested in four replicates using one lot of ARCHITECT *i*Gentamicin reagents and calibrators, and one lot of commercially available controls on one instrument. Three sample sets were tested each within a single run. The results were averaged and compared to the expected concentrations. The individual % differences were calculated and support the sponsor's claimed measuring range. **A summary of observed vs.**

expected concentrations are presented in the following table:

Pool No.	Expected Concentration (µg/mL)	Observed Mean (µg/mL)	% Difference
1	10.95	10.95	0.00
2	9.86	9.82	-0.33
3	8.76	8.73	-0.31
4	6.57	6.64	1.10
5	4.38	4.24	-3.20
6	2.19	2.14	-2.51
7	1.10	1.07	-2.51
8	0.55	0.54	-1.83
9	0.22	0.22	-0.68
10	0.11	0.10	-8.68
11	0.00	0.00	N/A

Recovery Study:

A study was conducted to demonstrate that gentamicin spiked into human serum can be accurately recovered by the ARCHITECT *i*Gentamicin assay. Twelve normal human specimens were obtained which contained no detectable amounts of gentamicin. These specimens were spiked with gentamicin stock solution to create test samples at concentrations of 2.5, 4.0, 6.0, and 8.0 µg/mL. Reference samples were created by spiking the twelve normal human specimens with diluent at the same volume used to create the test samples. The test (spiked) and reference (pre-spiked) samples were tested in four replicates. The percent recovery was calculated by the equation:

$$\% \text{ Recovery} = \frac{(\text{Mean Spiked Test Conc.} - \text{Mean Pre-Spiked Conc.})}{\text{Added (Spiked) Analyte Conc.}} \times 100\%$$

The mean % recovery was 95.7 and the individual % recovery results ranged from 91.1 to 99.2. Results are summarized in the following table:

Known analyte concentration (µg/mL)	Observed Mean (µg/mL)	Average (N=4) % Recovery
2.5	2.49	99.2
2.5	2.45	98.0
2.5	2.46	98.3
4.00	3.81	95.2
4.00	3.83	95.6

4.00	3.86	96.4
6.00	5.93	98.9
6.00	5.59	93.2
6.00	5.71	95.1
8.00	7.63	95.4
8.00	7.38	92.3
8.00	7.29	91.1

Validation of the manual dilution procedure:

A study was conducted to verify the use of ARCHITECT *i*Multi-Assay Manual Diluent as the manual diluent for routine 1:5 dilutions of a sample tested with the ARCHITECT *i*Gentamicin assay. Twelve serum/plasma samples were tested in replicates of three. The median % recoveries ranged between 91% and 109%.

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

The ARCHITECT *i*Gentamicin calibrators are traceable to United States Pharmacopeia (USP) gentamicin.

The ARCHITECT *i*Gentamicin Calibrators are prepared by gravimetric dilution of Gentamicin Reference Standard (USP) into recalcified plasma free of gentamicin. Each calibrator is tested by Relative Light Units (RLU) matching against the corresponding primary calibrator. The uncertainty in value assignments ranged in +/- 0.001 to 0.042 µg/mL.

Calibrator Stability:

The stability of the calibrators was established through real time testing conducted at multiple time points. For the real time closed vial testing, three lots of calibrators were stored continuously at 2 to 8 °C prior to testing at designated time points. At time point zero, all calibrator bottles were opened and closed, and then stored at 2-8 °C for the duration of the study. The serum panels were stored at -20°C or colder. Real time studies are on-going and scheduled to continue for 25 months (with a minimum of 6 months). Protocols and acceptance criteria were found adequate as presented in the 510(k).

d. Detection limit:

The Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were determined based on guidance from CLSI EP17-A.

Limit of Blank and Limit of Detection:

The limit of blank (LoB) and limit of detection (LoD) of the Architect iGentamicin assay were determined based on CLSI Protocol EP17-A. These evaluations were performed using one blank (N=200) and four low level gentamicin samples (N=320). Analysis yielded an LoB=0.00 µg/mL and LoD= 0.05 µg/mL. Two instruments, two lots of reagents, one lot of calibrators and one lot of controls were used for this study.

Limit of Quantitation:

Five zero-level samples and six samples with gentamicin concentrations (0.025, 0.05, 0.075, 0.1, 0.2, and 0.3 µg/mL) were tested in five separate runs over a minimum of 3 days using two reagent lots and two instruments. The LoQ was determined as the smallest concentration at which the total error was approximately 15 %. The LoQ was determined to be 0.2 µg/mL.

LoQ Summary

N	Target Conc. (µg/mL)	Mean Conc. (µg/mL)	% Bias	%CV	Observed % Total Error	LoQ (µg/mL)
200	0.20	0.19	7.4	4.0	15.4	0.20
200	0.30	0.28	7.6	3.2	14.0	

e. Analytical specificity:

The following compounds were tested for cross-reactivity or interference in samples containing 0 µg/mL, 2.5 µg/mL, and 7 µg/mL gentamicin.

Test samples were prepared by spiking each drug at the interferent concentration into each of the three gentamicin samples to yield test samples with different analyte levels (0, 2.5, 7.0 µg/mL). To compensate for any dilution effect, reference samples were prepared by adding diluent into human recalcified plasma that had been spiked with gentamicin to the target concentrations. The test and reference samples were tested with a minimum of 17 replicates using one lot of ARCHITECT iGentamicin reagents and calibrators and one lot of commercially available controls on one ARCHITECT i2000_{SR} instrument. Results are shown below and in the package insert:

Test Compound	Test Compound Concentration (µg/mL)	Gentamicin Concentration (µg/mL)				
		0.0	2.5		7.0	
		Conc. Diff.	Conc. Diff.	%difference	Conc. Diff.	% difference
Acetaminophen	200	0.00	0.03	0.0	0.08	0.0

Acetylcysteine	1,000	0.00	-0.01	0.0	0.01	0.0
Acetylsalicylic acid	300	0.00	-0.01	0.0	-0.34	-0.1
Amikacin	300	0.00	0.08	0.0	0.32	0.1
Amphotericin B	100	0.00	0.00	0.0	0.11	0.1
Ampicillin	50	0.00	-0.02	0.0	-0.36	-0.6
Ascorbic acid	30	0.00	-0.01	0.0	-0.03	-0.1
Carbenicillin	2,500	0.00	-0.33	0.0	-0.83	0.0
Cefamandole	250	0.00	-0.05	0.0	-0.08	0.0
Cefoxitin	1,000	0.00	-0.05	0.0	-0.21	0.0
Cephalexin	320	0.01	0.91	0.3	2.34	0.7
Cephalosporin C	1,000	0.00	0.02	0.0	0.06	0.0
Cephalothin	1,000	0.00	0.02	0.0	0.18	0.0
Chloramphenicol	250	0.00	-0.04	0.0	0.03	0.0
Clindamycin	2,000	0.00	0.00	0.0	0.00	0.0
Cyclosporine	6,000	0.00	0.10	0.0	0.59	0.0
Erythromycin	500	0.00	-0.12	0.0	0.24	0.0
Ethacrynic acid	400	0.00	0.04	0.0	-0.28	-0.1
5-Fluorocytosine	30	0.00	-0.01	0.0	-0.01	0.0
Furosemide	100	0.00	0.03	0.0	-0.40	-0.3
Fusidic acid	1,000	0.00	-0.04	0.0	-0.01	0.0
Ibuprofen	2,000	0.00	-0.01	0.0	-0.34	0.0
Kanamycin A	400	0.00	0.13	0.0	0.45	0.1
Kanamycin B	400	0.00	0.22	0.1	0.87	0.2
Levodopa	1,000	0.00	0.02	0.0	-0.03	0.0
Lincomycin	2,000	0.00	0.01	0.0	-0.02	0.0
Methicillin	200	0.00	-0.03	0.0	-0.15	-0.1
Methotrexate	50	0.00	-0.01	0.0	-0.10	-0.2
Methylprednisolone	200	0.00	-0.02	0.0	-0.03	0.0
Metronidazole	1,000	0.00	0.00	0.0	0.19	0.0
Neomycin	100	0.00	0.15	0.1	1.01	0.9
Netilmicin	10	4.41	4.58	45.8	4.93	49.3
Oxytetracycline	2,000	0.00	0.04	0.0	0.02	0.0
Penicillin V	10	0.00	0.00	0.0	0.08	0.7
Phenylbutazone	1,000	0.00	0.00	0.0	-0.06	0.0
Prednisolone	12	0.00	0.03	0.2	-0.04	-0.3
Rifampin	50	0.00	0.01	0.0	0.00	0.0
Sisomicin	10	3.29	3.29	27.4	3.78	31.5
Spectinomycin	100	0.00	-0.09	-0.1	-0.23	-0.2
Streptomycin	400	0.03	0.03	0.0	0.21	0.0
Sulfadiazine	1,000	0.00	-0.03	0.0	-0.02	0.0
Sulfamethoxazole	400	0.00	-0.01	0.0	0.20	0.0
Tetracycline	2,000	0.00	0.10	0.0	0.59	0.0
Theophylline	200	0.00	0.01	0.0	0.14	0.1
Ticarcillin	100	0.00	-0.02	-0.2	-0.09	-0.1
Tobramycin	100	0.00	0.28	0.2	0.84	0.7

Trimethoprim	20	0.00	0.01	0.0	-0.09	-0.4
Vancomycin	400	0.00	0.03	0.0	-0.06	0.0

Cephalexin, Netilmicin, and Sisomicin are included in the Limitations section of the ARCHITECT *i*Gentamicin package insert as drugs that will yield falsely elevate values for gentamicin. Although Sagamicin was not available for testing, it is also included in the Limitations section because it is structurally similar to gentamicin.

Interference from endogenous compounds was evaluated based on the CLSI EP7-A2 document. Two levels of gentamicin were tested: 2.5 and 7.0 µg/mL. The spiked samples were compared to the control samples. Results are summarized in the following table:

Potentially Interfering Endogenous Substance	Interferent Concentration	% Interference	
		2.5 µg/mL	7.0 µg/mL
Bilirubin	20 mg/dL	-0.6	0.7
Hemoglobin	500 mg/dL	2.7	3.4
Total Protein	12 g/dL	0.9	4.8
Triglycerides	3000 mg/dL	-1.6	0.4

Evaluation of other potentially interfering compounds:

Normal human serum pool and samples containing the clinical conditions listed below were spiked at two levels of gentamicin (2.5 and 7.0 µg/mL). Gentamicin concentrations of the spiked samples were compared to the samples without gentamicin. Results are summarized in the following table:

Potentially Interfering Clinical Condition	N	% Recovery Range (Individual)	
		2.5 µg/mL	7.0 µg/mL
Human Anti-Mouse Antibodies (HAMA)	12	99.4-107.1	91.2-103.7
Heterophilic Antibodies	12	97.6-107.9	87.6-105.2
Rheumatoid Factor	12	95.8-105.6	93.2-101.5

$$\% \text{Recovery} = \frac{\text{Post-Spike Result} - \text{Pre-Spike Result}}{\text{Result of Spiked Normal Serum Samples}} \times 100$$

f. Assay cut-off:

Not Applicable. This is a quantitative assay.

2. Comparison studies:

a. *Method comparison with predicate device:*

Method comparison was performed based on the CLSI EP9A-2 guideline. Samples used for the method comparison study were de-identified, leftover samples obtained from external vendors with gentamicin concentrations between 0.3 to 10.0 µg/mL. For the ARCHITECT *i*Gentamicin assay, the specimens were tested using three lots of reagents, one lot of calibrators, and one lot of commercially available controls and two ARCHITECT *i*2000_{SR} instruments. A total of 146 samples were tested in replicates of two. For the predicate method, specimens were tested using one lot of reagents, calibrators, and controls using one AxSYM instrument. Results ranged from 0.31 to 8.82 µg/mL with the ARCHITECT *i*Gentamicin assay and from 0.46 to 9.23 µg/mL with the AxSYM gentamicin assay. Results are summarized in the table below:

ARCHITECT	AxSYM	R	Intercept (µg/mL)	Slope
0.31 – 8.82 µg/mL	0.46-9.23 µg/mL	0.993	-0.04	0.96

b. *Matrix comparison:*

A study was conducted to evaluate different anticoagulant tube types that can be used with the ARCHITECT *i*Gentamicin assay. Twenty sample sets were collected for this study and a comparison was performed between the control tube (serum, plastic tube) and each of the blood collection tube types. The following blood collection tube types were tested : Glass tubes : serum, sodium EDTA; Plastic tubes : serum, lithium heparin, sodium heparin, and K2EDTA. Sample sets were spiked with gentamicin stock solution to yield the following target concentrations : 0.5, 1.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 µg/mL. The sample sets were tested on one ARCHITECT *i*2000_{SR} instrument in replicates of four using one lot of reagents, calibrators, and commercially available controls. The 95% confidence intervals around the mean % recovery for each tube type fell within 90-110% recovery.

The individual recoveries for each tube type are as follows :

Serum (glass) : 93.6 to 103.3%

Sodium heparin : 87.6 to 103.1%

Lithium heparin : 89.6 to 103%

Sodium EDTA : 90.3 to 99.1%

Dipotassium EDTA : 87.7 to 98.2%

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 provided values cited from the literature* as follows:

Peak serum levels of gentamicin in the range of 5 to 10 µg/mL are suggested for optimal therapeutic effectiveness. Sponsor states that trough levels greater than 2 µg/mL have been associated with renal failure in some patients.

*Keller F, Borner K, Schwarz A, Offermann G, Lode H. Therapeutic Aminoglycoside Monitoring in Renal Failure Patients, Therapeutic Drug Monitoring 9(2):148-153, June 1987

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.