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

A. 510(k) Number:

k102668

B. Purpose for Submission:

To obtain a substantial equivalence determination for Etest® strip for determining susceptibility of *Staphylococcus aureus*, *Enterobacteriacea*, and *Pseudomonas aeruginosa* to Tobramycin

C. Measurand:

Tobramycin concentrations of 0.0.16 – 256 μg/mL and 0.064 – 1024 μg/mL

D. Type of Test:

Etest® is a quantitative Antimicrobial Susceptibility Test (AST) growth based detection method.

E. Applicant:

AB bioMerieux

F. Proprietary and Established Names:

Etest® Tobramycin for Antimicrobial Susceptibility Testing

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test (AST) Powder

2. Classification:

   II

3. Product code:

   JWY - Manual Antimicrobial Susceptibility Test Systems

4. Panel:

   83 Microbiology

H. Intended Use:

1. Intended use(s):

   Etest® is a quantitative technique for determination of antimicrobial susceptibility of both non-fastidious Gram-negative and Gram positive aerobic bacteria such as *Enterobacteriaceae*, *Pseudomonas*, *Staphylococcus* and *Enterococcus* species and fastidious bacteria, such as anaerobes, *N. gonorrhoeae*, *S. pneumoniae*, *Streptococcus* and *Haemophilus* species. The system comprises a predefined antibiotic gradient which is used to determine the Minimum Inhibitory Concentration (MIC) in µg/mL of different antimicrobial agents against microorganisms as tested on agar media using overnight incubation.

2. Indication(s) for use:

   Etest® is a quantitative technique for determination of antimicrobial susceptibility of both non-fastidious Gram-negative and Gram positive aerobic bacteria such as *Enterobacteriaceae*, *Pseudomonas*, *Staphylococcus* and *Enterococcus* species and fastidious bacteria, such as anaerobes, *N. gonorrhoeae*, *S. pneumoniae*, *Streptococcus* and *Haemophilus* species. The system comprises a predefined antibiotic gradient which is used to determine the Minimum Inhibitory Concentration (MIC) in µg/mL of different antimicrobial agents against microorganisms as tested on agar media using overnight incubation.

   This 510(k) submission is for Etest® Tobramycin for MIC determination across concentrations of 0.016 – 256 µg/mL and 0.064 – 1024 µg/mL with *S. aureus*, *Enterobacteriacea*, and *P. aeruginosa*.

3. Special conditions for use statement(s):

   For prescription use

4. Special instrument requirements:

   Manual readings only

I. Device Description:

Etest® consists of a thin, inert and non-porous plastic strip, 5mm wide and 60 mm long. One side of the strip carries a two-letter code designating the identity of the antibiotic and is calibrated with MIC values in terms of µg/mL. A predefined exponential gradient of the dried and stabilized antibiotic covers a continuous

concentration range across 15 two-fold dilutions of a conventional MIC method.

The MIC interpretive criteria for tobramycin are as follows:

MIC (μg/mL)	Interpretation*
≤ 4	Susceptible (S)
8	Intermediate (I)
≥ 16	Resistant (R)

*S = Susceptible: Attainable levels in blood or tissue on usual usage, including oral administration when applicable.
I = Intermediate: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated (e.g. quinolones and B-lactams in urine), or when a higher than normal dosage of drug can be used (e.g. B-lactams). The "intermediate" category also includes a "buffer zone" which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.
R = Resistant to usually achievable systemic concentrations.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Etest®

2. Predicate 510(k) number(s):
   k913459

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Incubation Temperature	35°	Same
Inoculation	Isolated colonies from culture used	Same
Result	MIC	MIC
Incubation Atmosphere	Aerobic	Aerobic

Differences		
Item	Device	Predicate
Antibiotic	Tobramycin	Other antibiotics

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

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071462.pdf

2. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacterial That Grow Aerobically, Approved Standard, Document M07-A8.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing Approved Standard, Document M100-S19.

L. Test Principle:

The Etest® gradient technology is based on a combination of the concepts of dilution and diffusion test methods for susceptibility testing. Etest® directly quantifies antimicrobial susceptibility in terms of discrete MIC values. When the Etest® strip is applied to an inoculated agar plate, the antibiotic is immediately released from the plastic surface into the agar. A predefined, continuous gradient of antibiotic concentrations is created and maintained directly underneath the strip. After incubation whereby bacterial growth becomes visible, a symmetrical inhibition ellipse centered along the strip will be seen. The MIC value in ug/mL is read where the ellipse edge intersects the strip. Since Etest® generates MIC values which fall between two-fold dilutions for interpretation; the MIC value read must be recorded to the next two-fold dilution.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was conducted at three study sites. Twenty-five *Staphylococcus aureus*, 25 *Enterobacteriacea*, and 25 *P. aeruginosa* were tested at each site. Reference method plates were read visually in accordance with CLSI standard. Reproducibility was calculated as the percent of results for the combined sites which were within +/- one doubling dilution of the mode MIC value for all sites.

For the sake of reproducibility calculations, off-scale values are handled in two ways; “best case” and “worst case” scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode

MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value. There was no off-scale results with any of the groups of organisms tested in this study. So, only one value for reproducibility is reported.

Organism Group	Etest Concentration Range (µg/mL)	% Agreement (n/N) within +/- dilution
S. aureus	0.16 – 256	98.7 (74/75)
Enterobacteriacea	0.16 – 256	96.0 (72/75)
P. aeruginosa	0.064 – 1024	98.7 (74/75)

b. *Linearity/assay reportable range:*
Not applicable

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

The recommended QC isolates were tested a sufficient number of times with acceptable results with the reference method. The Etest® results demonstrate that the system can produce QC results in the recommended range.

Tobramycin quality control data from combined sites is shown below. At least 20 test results per organism at each site were available.

Tobramycin quality control data for Gram positive and Gram negative aerobic bacteria – combined sites:

QC Organism	MIC range (µg/mL)	MIC value (µg/mL)	Reference Frequency	Etest Frequency
S. aureus ATCC 29213	0.125 - 1	0.06	0	0
		0.125	2	0
		0.25	33	13
		0.5	22	47
		1	5	2
		2	0	0
E. faecalis ATCC 29212	8-32	4		
		8	18	8
		16	26	39
		32	20	17
		64	0	0

QC Organism	MIC range (μg/mL)	MIC value (μg/mL)	Reference Frequency	Etest Frequency
E. coli ATCC 25922	0.25 – 1	0.125		
		0.25	0	0
		0.5	33	25
		1	27	37
		2	0	0
P. aeruginosa ATCC 27853	0.25-1	0.125	0	0
		0.25	0	0
		0.5	58	39
		1	4	23
		2	0	0

All QC values were in the expected range.

A 0.5 McFarland was used to prepare inoculum for the reference dilution method and Etest inoculum. Colony count was performed periodically at each site to verify that the inoculum density was in the expected CFU/mL.

Inoculum density control for QC organisms ranged between 0.1 $X10^7$ CFU/mL and 0.4 X 10^8 CFU/mL for direct inoculum E-test, between 0.9$X10^7$ CFU/mL and 2.1 $X10^7$ CFU/mL for the reference agar dilution method and between 0.1$X10^5$ CFU/mL and 1.1 $X10^6$ CFU/mL for the reference broth dilution method.

The growth rate was 100% for all organisms tested.

d. Detection limit:
Not Applicable

e. Analytical specificity:
Not Applicable

f. Assay cut-off:
Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

CLSI recommended reference methods were used to determine susceptibility. Clinical testing was performed at three sites. Etest and reference broth microdilution and agar dilution methods were performed (internal site performed broth microdilution, while the two external sites performed the

reference agar dilution).

Clinical testing was performed on 1075 stock and fresh clinical isolates. In total, 711 isolates were freshly collected clinical isolates representing 66.1% of the total. In addition, a set of 225 challenge isolates was tested.

Performance was compared to the CLSI reference method. The performance evaluations are shown in the following tables.

Summary of essential and category agreement results for Challenge and Clinical strains

S. aureus

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	350	348	99.4	324	320	98.8	314	96.9	56	0	0	10
Challenge	75	73	97.3	37	37	100.0	37	100.0	43	0	0	0
Both	425	421	99.1	361	357	98.9	351	97.2	99	0	0	10

Enterobacteriacea

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	375	365	97.3	365	355	97.3	355	97.3	64	0	0	10
Challenge	75	74	98.7	73	72	98.6	68	93.2	14	0	0	5
Both	450	439	97.6	438	427	97.5	423	96.6	78	0	0	15

P. aeruginosa

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	350	350	100.0	347	347	100.0	343	98.8	77	0	0	4
Challenge	75	75	100.0	73	73	100.0	72	98.6	25	0	0	1
Both	425	425	100.0	420	420	100.0	415	98.8	102	0	0	5

ALL ISOLATES

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	1075	1063	98.9	1036	1022	98.6	1012	97.7	197	0	0	24
Challenge	225	222	98.7	183	182	99.5	177	96.7	82	0	0	6
Both	1300	1285	98.8	1219	1204	98.8	1189	97.5	279	0	0	30

EA-Essential Agreement **CA-**Category Agreement **R-**Resistant isolates.

Essential agreement (EA) is when the Etest® agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the Etest® result interpretation agrees exactly with the reference panel result interpretation based on interpretive criteria.

Summary of essential and category agreement results for Challenge and Clinical strains (Updated)

Clinical data

Organism group	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
S. aureus	350	348	99.4	324	320	98.8	314	96.9	56	0	0	10
Enterobacteriacea	375	365	97.3	365	355	97.3	355	97.3	64	0	0	10
P. aeruginosa	350	350	100	347	347	100	343	98.8	77	0	0	4
TOTAL	1075	1063	98.9	1036	1022	98.6	1012	97.7	197	0	0	24

Challenge

S. aureus	75	73	97.3	37	37	100	37	100	43	0	0	0
Enterobacteriacea	75	74	98.7	73	72	98.6	68	93.2	14	0	0	5
P. aeruginosa	75	75	100	73	73	100	72	98.6	25	0	0	1
TOTAL	225	222	98.7	183	182	99.5	177	96.7	82	0	0	6

Clinical and Challenge Combined

All organisms	1300	1285	98.8	1219	1204	98.8	1189	97.5	279	0	0	30

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For 1075 fresh clinical/stock isolates, EA/CA for Etest were 98.9%, and 97.7%, respectively.

For 225 challenge organisms, the EA /CA for Etest were 98.7%, and 96.7%, respectively.

For 1300 clinical and challenge organisms combined, the EA /CA for Etest were 98.8%, and 97.5%, respectively.

A total of 279 organisms were classified as resistant to tobramycin and there were no maj or vmj errors seen.

b. Matrix comparison:

Not Applicable

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:

According to the FDA drug label, tobramycin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section of the label.

The MIC interpretive criteria for tobramycin are as follows:

MIC (µg/mL)	Interpretation
≤ 4	Susceptible (S)
8	Intermediate (I)
≥ 16	Resistant (R)

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.