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

A. 510(k) Number:

k093604

B. Purpose for Submission:

To obtain a substantial equivalence determination for Etest® strip for determining susceptibility of anaerobic organisms to moxifloxacin

C. Measurand:

Moxifloxacin concentrations of 0.002 – 32 µg/mL

D. Type of Test:

Etest® is a quantitative Antimicrobial Susceptibility Test (AST) growth based detection method. The Etest strip contains a predefined exponential gradient of antibiotic and has the MIC reading scale in µg/mL. The gradient covers a continuous concentration range across 15 two-fold dilutions of a conventional MIC method.

E. Applicant:

AB BioMerieux

F. Proprietary and Established Names:

Etest® Moxifloxacin 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 the addition of the antibiotic moxifloxacin at concentrations of 0.002 – 32 µg/mL to the Etest® strip for testing of *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Clostridium perfringens*, and *Peptostreptococcus* spp.

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.

For anaerobic bacteria, the MIC interpretive criteria for moxifloxacin are as follows:

MIC (µg/mL)	Interpretation*
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	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):
   k000298

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

Differences		
Item	Device	Predicate
Antibiotic	Moxifloxacin	Other antibiotics

Differences		
Item	Device	Predicate
Incubation Atmosphere	Anaerobic	Aerobic and microaerophilic

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. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria, Approved Standard - 7th Edition, Document M11-A7

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 seven anaerobic organisms (11 *B. fragilis*, 10 *B. thetaiotaomicrons*, 3 *C. perfringens*, and 3 *Peptostreptococcus* species) 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 were no off-scale results in this study. So, only one value for overall reproducibility is reported.

The overall reproducibility was 100% for 27 organisms with on-scale results tested by Etest at 3 sites.

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.

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

QC Organism	MIC range (µg/mL)	MIC value (µg/mL)	Reference Frequency	Etest Frequency
B. fragilis ATCC 25285 Acceptable MIC range: 0.12 - 0.5 µg/mL	0.12 - 0.5	0.06	0	0
		0.125	47	9
		0.25	21	59
		0.5	0	0
		1	0	0
B. thetaiotaomicron ATCC 29741 Acceptable MIC range: 1 - 4 µg/mL	1 - 4	0.5	0	0
		1	35	30
		2	33	35
		4	0	2
		8	0	0
E. lentum ATCC 43055 Acceptable MIC range: 0.12 - 0.5 µg/mL	0.12 - 0.5	0.06	0	0
		0.125	32	40
		0.25	34	26
		0.5	2	
		1	0	0
C. difficile ATCC 700057 Acceptable MIC	1 - 4	0.5	0	0
		1	20	43
		2	46	22

range: 1-4 µg/mL		4	0	0
		8	0	0

All QC values were in the expected range. Etest results with *B. fragilis* tended towards a one doubling dilution higher than the reference standard.

A 0.5 McFarland was used to prepare inoculum for reference agar dilution method. A 1.0 McFarland standard was prepared for the 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 $0.7X10^8$ CFU/mL and $2.7 X 10^8$ CFU/mL for direct inoculum E-test and between $0.7X10^8$ CFU/mL and $1.6 X10^8$ CFU/mL for the reference agar 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:

The CLSI recommended agar dilution was used as the reference method to determine susceptibility. Clinical testing was performed at three sites. Etest and reference agar dilution were set up on *Brucella* blood agar (*Brucella* agar with 5% blood and 1% hemin and vitamin k).

Clinical testing was performed on 418 anaerobic stock and fresh clinical isolates (207 *B. fragilis*, 116 *B. thetaiotaomicrons*, 61 *C. perfringens*, and 34 *Peptostreptococcus* species). In total, 213 isolates were freshly collected clinical isolates representing 51% of the total.

In addition, a set of 53 challenge isolates was tested (25 *B. fragilis*, 21 *B. thetaiotaomicron*, 4 *C. perfringens*, and 3 *Peptostreptococcus* species).

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

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

B. fragilis

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	207	200	96.6	196	189	96.4	179	91.3	10	0	0	17
Challenge	25	24	96.0	25	24	96.0	23	92.0	3	0	0	2
Both	232	224	96.6	221	213	96.4	202	91.4	13	0	0	19

B. thetaiotaomicron

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	116	115	99.1	108	107	99.1	99	91.7	8	0	1	8
Challenge	21	19	90.5	20	18	90.0	17	85.0	2	0	0	3
Both	137	134	97.8	128	125	97.7	116	90.6	10	0	1	11

C. perfringens

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	61	60	98.4	61	60	98.4	59	96.7	0	0	0	2
Challenge	4	4	100	4	4	100	4	100	0	0	0	0
Both	65	64	98.5	65	64	98.5	63	96.9	0	0	0	2

***Peptostreptococcus* spp.**

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	34	30	88.2	33	29	87.9	32	97.0	2	0	0	1
Challenge	3	2	66.7	3	2	66.7	2	66.7	1	0	0	1
Both	37	32	86.5	36	31	86.1	34	94.4	3	0	0	2

ALL ISOLATES

	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#R	#vmj	#maj	#min
Clinical	418	405	96.9	398	385	96.7	369	92.7	20	0	1	28
Challenge	53	49	92.5	52	48	92.3	46	88.5	6	0	0	6
Both	471	454	96.4	450	433	96.2	415	92.2	26	0	1	34

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
B. fragilis	207	200	96.6	196	189	96.4	179	91.3	10	0	0	17
B. thetaiotaomicron	116	115	99.1	108	107	99.1	99	91.7	8	0	1	8
C. perfringens	61	60	98.4	61	60	98.4	59	96.7	0	0	0	2
Peptostreptococcus spp.	34	30	88.2	33	29	87.9	32	97.0	2	0	0	1
TOTAL	418	405	96.9	398	385	96.7	369	92.7	20	0	1	28

Challenge

B. fragilis	25	24	96.0	25	24	96.0	23	92.0	3	0	0	2
B. thetaiotaomicron	21	19	90.5	20	18	90.0	17	85.0	2	0	0	3
C. perfringens	4	4	100	4	4	100	4	100	0	0	0	0
Peptostreptococcus spp.	3	2	66.7	3	2	66.7	2	66.7	1	0	0	1
TOTAL	53	49	92.5	52	48	92.3	46	88.5	6	0	0	6

Clinical and Challenge Combined

All organisms	471	454	96.4	450	433	96.2	415	92.2	26	0	1	34

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For 418 fresh clinical/stock isolates, the EA/CA for Etest were 96.7%, and 92.7%, respectively.

For 53 challenge organisms, the EA /CA for Etest were 92.5%, and 88.7%, respectively. The CA of 88.7% is acceptable in light of a very good EA and the occurrence of only minor discrepancies (i.e. no maj or vmj discrepancies).

For 471 clinical and challenge organisms combined, the EA /CA for Etest were 96.2%, and 92.2%, respectively.

A total of 26 organisms were classified as resistant to moxifloxacin 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, Moxifloxacin has been shown to be active against most strains of the following anaerobic microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section of the label.

Bacteroides fragilis
Bacteroides thetaiotaomicron
Clostridium perfringens
Peptostreptococcus species

For the above anaerobic bacteria, the MIC (μg/mL) interpretive criteria for moxifloxacin are as follows:

≤ 2 Susceptible (S); 4 Intermediate (I) ; ≥ 8 Resistant (R)

The Interpretative criteria, QC isolates and the expected ranges are the same as recommended by the CLSI and the FDA. However, the FDA drug label does not provide QC ranges or interpretive criteria for *Clostridium difficile*.

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.