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

A. 510(k) Number:

k151873

B. Purpose for Submission:

To obtain clearance for the addition of ceftaroline at concentrations 0.002 – 32 µg/mL to the Etest strip for susceptibility testing of fastidious species (S. *pneumoniae, S. agalactiae, Haemophilus influenzae*).

C. Measurand:

Ceftaroline 0.002 – 32µg/mL

D. Type of Test:

Quantitative AST growth based detection

E. Applicant:

bioMérieux, Inc

F. Proprietary and Established Names:

Etest® Ceftaroline (0.002 – 32 µg/mL)

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   II

3. Product code:

   JWY - Manual Antimicrobial Test Systems

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended use(s):

   Etest® is a quantitative technique for determining the antimicrobial susceptibility testing of 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 determining the antimicrobial susceptibility testing 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 submission is for the additional indications for the antimicrobial Etest Ceftaroline at concentrations of 0.002 – 32 µg/mL. Etest® Ceftaroline has been shown to be active *in vitro* against fastidious strains of the microorganisms listed below, according to the FDA label for this antimicrobial agent:

   Streptococcus pneumoniae
   Streptococcus agalactiae
   Haemophilus influenzae

3. Special conditions for use statement(s):

   For prescription use

   Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

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 current FDA pharmaceutical drug label includes the following indicated fastidious organisms:

[S. agalactiae (skin isolates only), S. pneumoniae and H. influenzae (Community Acquired Bacterial Pneumonia isolates only)] S= ≤ 0.5 µg/mL*

*The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Etest® Ceftaroline

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

   k121002

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Antibiotic	Ceftaroline 0.002-32 µg/mL	Same
Incubation	35°; 5% CO_2; 20-24 hours	Same
Inoculation	Isolated colonies from culture used	Same
Result	MIC	Same
Concentration Range	0.002 – 32 µg/mL	Same

Differences		
Item	Device	Predicate
Organisms	*Community-Acquired Bacterial Pneumonia (CABP):* *Streptococcus pneumoniae* *Haemophilus influenzae* *Skin infections:* *Streptococcus agalactiae*	Skin infections: *Staphylococcus aureus* (including methicillin-susceptible and resistant isolates)
Reading time	Etest compared to Broth Microdilution reference method read at 18 and at 23 hours	Etest results compared to Broth Microdilution reference method read at 16-20 hours.

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

"Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA";

CLSI M7-A9 "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, January 2009"

CLSI M100-S24"Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement, January 2011"

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 µg/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. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

Twenty-five isolates of each organism (*Haemophilus influenzae, Streptococcus agalactiae and Streptococcus pneumoniae*) were tested at three external sites to determine site to site reproducibility. Results were within +/- one doubling dilution agreement as compared to the mode MIC value of Ceftaroline for all organisms at all sites and there were no off-scale results. The results were acceptable and demonstrated ≥ 95% reproducibility.

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 (Tables 1 and 2).

Table 1. Quality Control Data Read at 18 hours

ORGANISM	**conc.**	**Reference Frequency**	**Etest® Frequency**
Haemophilus influenzae ATCC 49247 Expected Results 0.032-0.125	<0.032	1	
	0.032	7	4
	0.0.064	74	38
	0.125	5	50
	>0.125		1
Streptococcus pneumonia ATCC 49619 Expected Results 0.008-0.032	<0.008		
	0.008	23	1
	0.016	75	35
	0.032	5	88
	>0.032		2

Table 2. Quality Control Data Read at 23 hours

ORGANISM	**conc.**	**Reference Frequency**	**Etest® Frequency**
Haemophilus influenzae ATCC 49247 Expected Results 0.032-0.125	<0.032		
	0.032	7	4
	0.0.064	74	48
	0.125	6	50
	>0.125		1
Streptococcus pneumonia ATCC 49619 Expected Results 0.008-0.032	<0.008		
	0.008	6	1
	0.016	92	35
	0.032	5	88
	>0.032		3

The quality control results are acceptable.

The inoculum was prepared to match a 0.5 McFarland. Colony counts were performed periodically at each site to demonstrate that the inoculum procedure results were in the expected CFU/mL.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

Clinical testing was performed at three external and one internal sites. There were 694 clinical isolates, of which 225 were stock (31.7%), and a challenge set of 50 isolates of each organism claimed (*H. influenzae, S. agalactiae and S. pneumoniae*). A total of 150 challenge isolates was evaluated.

a. Method comparison with predicate device:

The CLSI recommended broth dilution reference panel was prepared and interpreted according to CLSI recommendations with the following modification: broth microdilution panels were read at 18 hours as indicated in the FDA approved pharmaceutical drug label for Ceftaroline. The 18 hour incubation is required due to degradation of Ceftaroline activity when incubation extends to 24 hours. Panels were re-incubated and read at 23 hours per the CLSI recommendation of 20-24 hour incubation.

Etest was performed following Table 1 (Recommended Media and Inoculum) of the Generic Package Insert: *Streptococcus pneumoniae* and *Streptococcus agalactiae* were inoculated onto Mueller Hinton agar + 5% blood; *Haemophilus influenzae* isolates were inoculated onto HTM agar media. Isolated colonies from an overnight agar plate were emulsified in Mueller Hinton or HTM broth to achieve the specified inoculum turbidity compared to a 0.5 McFarland turbidity standard. In this submission, the suspension prepared in broth was used within 15 minutes of preparation. Testing conditions consisted of incubation at 35°C; 5% CO_2 for 20-24 hours. All

isolates grew in the clinical and challenge studies.

The clinical testing included both fresh clinical isolates and stock isolates along with a challenge set with known results. The following footnote was added to the package insert:

> "*Refer to the FDA approved pharmaceutical antimicrobial agent package insert for interpreting and reporting results of Ceftaroline which has been shown to be active against the following organisms/corresponding clinical infections: Streptococcus agalactiae (skin infections isolates only), S. pneumoniae and H. influenzae (community acquired bacterial pneumonia isolates only)".*

A comparison was provided to the reference method with the following agreement (Tables 3 through 6).

Table 3. Summary for Fastidious Species
(Etest Compared to Reference Method Read at 18 Hours)

	EA Tot	EA #	EA%	Eval EA tot	Eval EA#	Eval EA %	CA#	CA%	NS	vmj	maj	min
Clinical	694	645	92.9	677	639	94.4	694	100	0	0	0	NA
Challenge	150	148	98.7	146	145	99.3	150	100	0	0	0	NA
Combined	844	793	94.0	823	784	95.3	844	100	0	0	0	NA

Table 4. Summary for Fastidious Species
(Etest Compared to Reference Method Read at 23 Hours)

	EA Tot	EA #	EA%	Eval EA tot	Eval EA#	Eval EA %	CA#	CA %	NS	vmj	maj	min
Clinical	694	662	95.4	687	658	95.8	694	100	0	0	0	NA
Challenge	150	149	99.3	147	146	99.3	150	100	0	0	0	NA
Combined	844	811	96.1	834	804	96.4	844	100	0	0	0	NA

Table 5. Performance of Clinical and Challenge Isolates by Species
(Reference Method Read at 18 hours)

	TOT	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA N	CA %	No. NS	min	maj	vmj
Streptococcus pneumoniae												
Clinical	233	219	94.0	231	218	94.4	233	100	0	NA	0	0
Challenge	50	50	100	50	50	100	50	100	0	NA	0	0
Combined	283	269	95.1	281	268	95.4	283	100	0	NA	0	0
Streptococcus agalactiae												
Clinical	226	209	92.5	219	208	95.0	226	100	0	NA	0	0
Challenge	50	50	100	50	50	100	50	100	0	NA	0	0
Combined	276	259	93.8	269	258	95.9	276	100	0	NA	0	0
Haemophilus influenzae												
Clinical	235	217	92.3	227	213	93.8	235	100	0	NA	0	0

Challenge	50	48	96.0	46	45	97.8	50	100	0	NA	0	0
Combined	285	265	93.0	273	258	94.50	285	100	0	NA	0	0

Table 6. Performance of Clinical and Challenge Isolates by Species (Reference Method Read at 23 hours)

	TOT	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA N	CA %	No. NS	min	maj	vmj
Streptococcus pneumoniae												
Clinical	233	222	95.3	231	221	95.7	233	100	0	NA	0	0
Challenge	50	50	100	50	50	100	50	100	0	NA	0	0
Combined	283	272	96.1	281	271	96.4	283	100	0	NA	0	0
Streptococcus agalactiae												
Clinical	226	219	96.9	225	219	97.3	226	100	0	NA	0	0
Challenge	50	50	100	50	50	100	50	100	0	NA	0	0
Combined	276	269	97.5	275	269	97.8	276	100	0	NA	0	0
Haemophilus influenzae												
Clinical	235	221	94.0	231	218	94.4	235	100	0	NA	0	0
Challenge	50	49	98.0	47	46	97.9	50	100	0	NA	0	0
Combined	285	270	94.7	278	264	95.0	285	100	0	NA	0	0

EA-Essential Agreement **CA**-Category Agreement **NS**-not susceptible isolates
min – minor discrepancies maj – major discrepancies vmj – very major discrepancies

Essential agreement (EA) is when the Etest® results 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.
The overall combined %EA and %CA consistently meet the acceptance criteria of greater than or equal to 90%.

MIC Trends:
Using the data provided by the sponsor in the diagonal table format recommended in the AST Guidance, an analysis was conducted to check for trending in MIC values.
A higher reading trend was observed in the overall performance of *S. agalactiae, S. pneumoniae and H. influenzae* compared to the CLSI broth micro-dilution method when read at 18 hours and 23 hours, as summarized in Tables 7 and 8 below respectively.

Table 7. Trending of Results in Combined Clinical and Challenge Study (Reference Method Read at 18 Hours)

Organism	Difference in MIC as Compared to the CLSI Reference Method							
	≤ -3	-2	-1	0	+1	+2	≥ +3	Total
S. agalactiae	0	0	2.9% (8/276)	53.6% (148/276)	37.3% (103/276)	6.1% (15/276)	0.7% (2/276)	276
S. pneumoniae	0	0	2.4% (7/283)	50.1% (142/283)	42.4% (120/283)	4.9% (13/283)	0.3% (1/283)	283
H. influenzae	0.35% (1/285)	0.7% (2/285)	8.07% (23/285)	48.07% (137/285)	36.8% (105/285)	4.5% (13/285)	1.4% (4/285)	285
Total	0.11% (1/844)	0.2% (2/844)	4.5% (38/844)	50.6% (427/844)	38.6% (328/844)	5.2% (41/844)	0.4% (7/844)	844

Table 8. Trending of Results in Combined Clinical and Challenge Study (Reference Method Read at 23 Hours)

Organism	Difference in MIC as Compared to the CLSI Reference Method							
	≤ -3	-2	-1	0	+1	+2	≥+3	Total
S. agalactiae	0	0	4.3% (12/276)	57.2% 158/276	35.8% (99/276)	2.5% (7/276)	0	276
S. pneumoniae	0	0	2.4% (7/283)	53.7% (152/283)	40% (113/283)	3.8% (11/283)	0	283
H. influenza	0.3% (1/285)	1.4% (4/285)	8.7% (25/285)	52% (148/285)	34.03% (97/285)	3.1% (9/285)	0.3% (1/285)	285
Total	0.1% (1/844)	0.4% (4/844)	5.2% (44/844)	54.2% (458/844)	36.6% (309/844)	3.1% (27/844)	0.1% (1/844)	844

This trending and the potential for occurrence of major error(s) for Ceftaroline when testing *S. agalactiae, S. pneumoniae and H. influenzae* with E-test was addressed in the labeling by adding the following footnote under the interpretation table in labeling:

"*MIC values for fastidious Gram positive organisms tended to be one or more doubling dilution higher compared to the CLSI broth microdilution method.*

The MIC results read at 18 hour were higher by one or more doubling dilution as follows: 43.4% (120/276) for S. agalactiae, 47.3% (134/283) for S. pneumoniae, and 42.8% (122/285) for H. influenzae. The MIC results read at 23 hours were higher by one or more doubling dilution as follows: 38.4% (106/276) for S. agalactiae, 43.8% (124/283) for S. pneumoniae, and 37.5% (107/285) for H. influenzae".

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:

Organism and Infection Source	**Interpretive Criteria**
Streptococcus agalactiae (skin isolates only)	S= ≤ 0.5 µg/mL**
Streptococcus pneumoniae (CABP* isolates only)	
Haemophilus influenzae (CABP isolates only)	

*Community Acquired Bacterial Pneumonia
**The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

The Interpretative criteria, QC isolates and the expected ranges are the same as recommended by the CLSI and the FDA. All values will be included in the package insert.

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.