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

A. 510(k) Number:

K183031

B. Purpose for Submission:

To obtain a substantial equivalence determination for Meropenem/Vaborbactam at concentrations of 0.004/8 – 64/8 µg/mL for susceptibility testing of Gram-negative aerobic microorganisms with ETEST.

C. Measurand:

Meropenem/Vaborbactam 0.004/8 – 64/8 µg/mL

D. Type of Test:

Quantitative AST growth-based detection

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

ETEST Meropenem/Vaborbactam (MEV) (0.004/8 – 64/8 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 manual, quantitative technique for determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-positive aerobic bacteria and fastidious bacteria. 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 tested on agar media after overnight incubation.

   Meropenem/Vaborbactam has been shown to be active against the Gram-negative aerobic microorganisms listed below according to the FDA label for this antimicrobial agent.

   ETEST MEV can be used to determine the MIC of Meropenem/Vaborbactam against the following microorganisms:

   Active both *in vitro* and in clinical infections:
   Enterobacter cloacae complex
   Escherichia coli
   Klebsiella pneumoniae

   In vitro data are available for the following microorganisms, but clinical significance is unknown:
   Citrobacter freundii
   Citrobacter koseri
   Klebsiella aerogenes
   Klebsiella oxytoca
   Morganella morganii
   Providencia spp.
   Serratia marcescens

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use only

   Limitation:

   - ETEST Meropenem/Vaborbactam (MEV) must not be used for susceptibility testing of *Proteus mirabilis.* When testing this organism, the EA did not meet

acceptance performance during comparative testing.

- The ability of the ETEST Meropenem/Vaborbactam to detect the following resistant *Enterobacteriaceae* isolates is unknown because resistant isolates were either not available or an insufficient number was encountered at the time of comparative testing: *C. freundii*, *C. koseri*. *K. aerogenes*, *E. cloacae* complex, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *M. morganii*, *P. rettgeri*, *P. stuartii*, and *S. marcescens*.

- The safety and efficacy of Meropenem/Vaborbactam in treating clinical infections due to bacteria other than *E. cloacae* complex*, E. coli,* and *K. pneumoniae* may or may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information in those instances is unknown.

4. Special instrument requirements:

   Not applicable

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 three letter code designating the identity of the antibiotic and is calibrated with MIC values in terms of µg/mL. On the reverse, 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.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ETEST Ceftazidime/Avibactam

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

   K172150

3. Comparison with predicate:

Table 1: Comparison with the Predicate Device

Item	Device K183031 ETEST Meropenem/Vaborbactam	Predicate K172150 ETEST Ceftazidime/Avibactam
Similarities		
Intended Use	ETEST is a manual, quantitative technique for determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-positive aerobic bacteria and fastidious bacteria. 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 tested on agar media after overnight incubation.	Same
Test Design	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.	Same
Inoculation	Isolated colonies from culture	Same
Incubation	35º±2º C for 16 – 20 hours	Same
Result	MIC	Same
Differences		
Antmicrobial Agent	Meropenem/Vaborbactam	Ceftazidime/Avibactam
Antmicrobial Concentration Range	0.004/8 – 64/8 µg/mL	0.016/4 – 256/4 µg/mL

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

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

CLSI M02-A12, Performance Standards for Antimicrobial Disk Susceptibility Test; Approved Standard, January 2015.

CLSI M07-A10, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, January 2015.

CLSI M100-28th ed., Performance Standards for Antimicrobial Susceptibility Testing; Volume 38, No. 1, January 2018.

L. Test Principle:

The ETEST consists of a thin, inert, nonporous plastic strip that is used to determine the antimicrobial susceptibility of bacteria. One side of the strip carries the minimum inhibitory concentration (MIC) reading scale expressed in µg/mL. The other side of the strip contains a predefined continuous gradient of antibiotic concentrations.

When the strip is applied to an inoculated agar surface, the preformed antibiotic gradient immediately transfers into the agar matrix, then forming a stable, continuous and exponential gradient of antibiotic concentrations directly underneath the strip. Bacteria growth becomes visible during incubation, and a symmetrical inhibition ellipse centered along the strip appears. After incubation, the MIC value is read from the scale in terms of µg/mL at complete inhibition of bacterial growth, where the pointed end of the ellipse 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.

The MIC gradient on ETEST Meropenem/Vaborbactam ranges from 0.004/8 – 64/8 µg/mL.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   A reproducibility study was conducted at three external sites using 10 isolates of Gram negative organisms that were consistent with the intended use. The isolates tested included *E. coli* (3), *K. pneumoniae* (3), *C. freundii* (1)*, K. aerogenes* (1), *E. cloacae* (1), and *S. marcescens* (1).

   Most of the results were within ± 1 doubling dilution of the MIC mode for Meropenem/Vaborbactam. The reproducibility was acceptable at 99.6%.

   b. Linearity/assay reportable range:

   Not applicable

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

   Inoculum Density Check. Inoculum density checks were performed for all quality control and reproducibility organism suspensions and for 10% of the suspensions prepared for susceptibility testing of the fresh clinical isolates.

   The mean inoculum density of *E. coli* ATCC 25922 was acceptable at 4.83×10^5 CFU/mL.

   Purity Check. All clinical, challenge and reproducibility test suspensions were subcultured to assure purity.

Growth or Device Failure. There were no growth or device failures during the course of the study.

Quality Control Testing. QC organisms for meropenem/vaborbactam recommended by both FDA and the CLSI were tested at four sites. The QC organisms tested included *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *K. pneumoniae* ATCC BAA-1705, and *P. aeruginosa* ATCC 27853. These QC strains were tested a minimum of 20 times per site by both the ETEST and the reference method. The results demonstrate that the meropenem/vaborbactam ETEST can produce quality control results in the recommended range > 95% of the time. See Table 2.1 below for summary of the QC results.

Table 2.1: Quality Control Summary for Meropenem/Vaborbactam

QC Organism	Meropenem/ Vaborbactam Expected Range (µg/mL)	Concentration (µg/mL)	Reference	ETEST
E. coli ATCC 25922	0.008/8 – 0.064/8	<0.008		
		0.008		
		0.016	32	85
		0.032	54	1
		0.064		
		>0.064		
K. pneumoniae ATCC 700603	0.016/8 – 0.064/8	<0.016		
		0.016		1
		0.032	69	70
		0.064	15	15
		>0.064	2	
K. pneumoniae ATCC BAA-1705	0.008/8 – 0.064/8	<0.008		
		0.008		
		0.016	24	17
		0.032	56	68
		0.064	5	1
		>0.064		
P. aeruginosa ATCC 27853	0.125/8 – 1/8	<0.125		
		0.125	5	1
		0.25	56	80
		0.5	19	4
		1	6	1
		>1		

Additionally and to ensure that the plasmid encoding β-lactamse has not been lost in QC isolate *K. pneumoniae* ATCC BAA-1705, this strain was tested using a meropenem alone. Testing was evaluated by disk diffusion method as recommended

by CLSI M100. Meropenem disk at concentration of 10 µg was tested at four sites and the results are shown in Table 2.2 below.

Table 2.2: Performance Summary of Meropenem- Disk Diffusion

QC Organism	Meropenem (10 µg) Expected Range (mm)	Zone size (mm)	Disk Reuslts
K. pneumoniae ATCC BAA-1705	11 – 18	<11	
		11	10
		12	13
		13	8
		14	9
		15	18
		16	9
		17	3
		18	
		>18	

Test results *K. pneumoniae* ATCC BAA-1705 with meropenem demonstrated the integrity of the QC isolate with 100% (70/70) of the results within the expected range.

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:

Results obtained with ETEST Meropenem/Vaborbactam were compared to results obtained with the CLSI broth microdilution reference panel. The CLSI panel was prepared and interpreted according to CLSI recommendations outlined in the CLSI Standard: CLSI Document M07-A10, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition, January 2015. The testing conditions for the reference method consisted of the following:

- Medium – Cation-adjusted Mueller Hinton Broth with appropriate dilutions of antimicrobial solution added
- Inoculum – Direct colony suspension to achieve a suspension equivalent to a

0.5 McFarland standard suspension
- Incubation 35 °C in ambient air; 16-20 hours for all organisms

Clinical testing was performed at four sites using a total of 550 clinical isolates. There were 313 fresh isolates (56.9%), 110 (20.0%) recent isolates, and 127 (23.1%) stock isolates. Clinical isolates were tested using both ETEST and the reference method. During the comparative testing, the EA performance of the 31 *P. mirabilis* isolates did not meet the acceptance criteria and therefore was removed from the dataset. As a result, there were a total of 519 clinical isolates after excluding the 31 *P. mirabilis* isolates. This organism was also removed from the indicated organisms in the indications for use statement.

A total of 79 challenge isolates were tested at a single site using ETEST and the reference method. The EA performance of the four *P. mirabilis* isolates also did not meet the acceptance criteria and was excluded from the calculation, resulting in a total of 75 challenge isolates after excluding the four *P. mirabilis* isolates .

The comparative study (both clinical and challenge) included 594 *Enterobacteriaceae* isolates. They were: *C. freundii* (32), *C. koseri* (32). *K. aerogenes* (33), *E. cloacae* spp. complex (98), *E. coli* (136), *K. oxytoca* (31), *K. pneumoniae* (128), *M. morganii* (31), *P. rettgeri* (21), *P. stuartii* (21), and *S. marcescens* (31).

Information on the *Enterobacteriaceae* isolates was added as a footnote to the performance table in the package insert:

> *The performance data presented for Enterobacteriaceae exclude Proteus mirabilis. There were C. freundii (32), C. koseri (32), K. aerogenes (33), E. cloacae complex (98), E. coli (136), K. oxytoca (31), K. pneumoniae (128), M. morganii (31), P. rettgeri (21), P. stuartii (21), and S. marcescens (31).*

The performance of the 594 clinical and challenge isolates is summarized in Table 3.

Table 3: Performance of *Enterobacteriaceae*, Excluding *P. mirabilis*

	Tot	No. EA	EA%	Eval Tot	No. Eval EA	Eval EA%	No. CA	CA%	No. R	min	maj	vmj
C. freundii												
Clinical	30	29	96.7	30	29	96.7	30	100	0	0	0	0
Challenge	2	2	100	2	2	100	2	100	0	0	0	0
Combined	32	31	96.9	32	31	96.6	32	100	0	0	0	0
C. koseri												
Clinical	30	29	96.7	30	29	96.7	30	100	0	0	0	0
Challenge	2	2	100	2	2	100	2	100	0	0	0	0
Combined	32	31	96.9	32	31	96.9	32	100	0	0	0	0
Klebsiella (Enterobacter) aerogenes												
Clinical	30	28	93.3	30	28	93.3	30	100	0	0	0	0
Challenge	3	3	100	3	3	100	3	100	0	0	0	0
Combined	33	31	93.9	33	31	93.9	33	100	0	0	0	0

	Tot	No. EA	EA%	Eval Tot	No. Eval EA	Eval EA%	No. CA	CA%	No. R	min	maj	vmj
***E. cloacae* complex**												
Clinical	90	90	100	90	90	100	90	100	0	0	0	0
Challenge	8	8	100	8	8	100	8	100	0	0	0	0
Combined	98	98	100	98	98	100	98	100	0	0	0	0
E. coli												
Clinical	120	116	96.7	119	116	97.5	120	100	0	0	0	0
Challenge	16	16	100	15	15	100	15	93.8	2	1	0	0
Combined	136	132	97.1	134	131	97.8	135	99.3	2	1	0	0
K. oxytoca												
Clinical	30	30	100	30	30	100	30	100	0	0	0	0
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
Combined	31	31	100	31	31	100	31	100	0	0	0	0
K. pneumoniae												
Clinical	88	86	97.7	87	85	97.7	88	100	1	0	0	0
Challenge	40	37	92.5	32	30	93.8	38	95.0	10	2	0	0
Combined	128	123	96.1	119	115	96.6	126	98.4	11	2	0	0
M. morganii												
Clinical	30	25	83.3	30	25	83.3	30	100	0	0	0	0
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
Combined	31	26	83.9	31	26	83.9	31	100	0	0	0	0
P. rettgeri												
Clinical	21	17	81.0	21	17	81.0	21	100	0	0	0	0
P. stuartii												
Clinical	20	18	90.0	20	18	90.0	20	100	0	0	0	0
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
Combined	21	19	90.5	21	19	90.5	21	100	0	0	0	0
S. marcescens												
Clinical	30	29	96.7	30	29	96.7	29	96.7	0	1	0	0
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
Combined	31	30	96.8	31	30	96.8	30	96.8	0	1	0	0
Enterobacteriaceae*, Excluding *P. mirabilis												
Clinical	519	497	95.8	517	496	95.9	518	99.8	1	1	0	0
Challenge	75	72	96.0	66	64	97.0	72	96.0	12	3	0	0
Combined	594	569	95.8	583	560	96.1	590	99.3	13	4	0	0

EA – Essential Agreement (+/- 1 dilution)
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential Agreement (EA) occurs when the result of the reference method and that of ETEST Meropenem/Vaborbactam are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both ETEST Meropenem/Vaborbactam and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of ETEST Meropenem/Vaborbactam.

Overall Performance:

The overall performance of the ETEST Meropenem/Vaborbactam for

Enterobacteriaceae, with *P. mirabilis* removed, is acceptable at 95.8% EA and 99.3% CA. There were no very major or major discrepancies; the minor discrepancy rate was 0.7% (4/594). There were 13 isolates (11 *K. pneumoniae* and 2 *E. coli*) that were resistant to Meropenem/Vaborbactam in the comparative studies. A limitation was included in the package insert:

> *The ability of the ETEST Meropenem/Vaborbactam to detect the following resistant Enterobacteriaceae isolates is unknown because resistant isolates were either not available or an insufficient number was encountered at the time of comparative testing: C. freundii, C. koseri. K. aerogenes, E. cloacae complex, E. coli, K. oxytoca, K. pneumoniae, M. morganii, P. rettgeri, P. stuartii, and S. marcescens.*

Inoculator and ETEST Strip Applicator Options

Culture media plates for ETEST are traditionally inoculated and streaked by swabs; ETEST strips are applied onto inoculated media by forceps. In the Meropenem/Vaborbactam studies, inoculator RETRO C80 was used at two sites and manual strip applicator, vacuum pen NEMA C88 was used at one site. The footnote below is added to the performance table in the package insert:

> *Optional inoculator and ETEST strip applicator were used for plate inoculation and applying ETEST strips onto agar media. In the studies, swab and Retro C80 were used for plate inoculation/streaking, forceps and vacuum pen NEMA C88 were used for ETEST strip applications.*

MIC Trends:

Using the combined claincal and challenge data for *Enterobacteriaceae,* an analysis of trending was conducted. Trending was assessed using current trending review criteria (i.e., ≥30% difference between higher and lower dilution readings). This trending calculation considers MIC values that are determined to be one or more doubling dilution lower or higher compared to the reference method irrespective whether the device MIC values are on-scale or not. The analysis is presented in Table 4.1 for *Enterobacteriaceae* excluding *P. mirabilis*.

Table 4.1: Trending Analysis for *Enterobacteriaceae* (Clinical and Challenge Combined), Excluding *P. mirabilis*

Total	≥2 dil lower	1 dil lower	Exact	1 dil higher	≥2 dil higher
Enterobacteriaceae ‡					
594	21	224	330	15	4
	245 (41.25%)		(55.56%)	19 (3.20%)	

‡ Percent difference between the higher and lower dilution trends for *Enterobacteriaceae* is: -38.05%; 95% CI (-42.21% to -33.78%)

NOTE: A negative percent difference value indicates lower MIC when compared to the reference method.

Trending was observed with *Enterobacteriaceae*. The difference between higher and lower dilutions was -38.05%. The following footnote was included in the labeling to address the trending:

> *ETEST Meropenem/Vaborbactam MIC values tended to be in exact agreement or at least one doubling dilution lower when testing Enterobacteriaceae compared to the CLSI reference broth microdilution.*

MIC trends for each intended *Enterobacteriaceae* species was also evaluated as noted in Table 4.2 below.

Table 4.2: Trending Analysis of *Enterobacteriaceae*, Excluding *P. mirabilis* (by species)

Total	≥2 dil lower	1 dil lower	Exact	1 dil higher	≥2 dil higher
C. freundii [a]					
32	1	4	27	0	0
	5 (15.63%)		(84.38%)	0 (0.00%)	
C. koseri [b]					
32	1	8	23	0	0
	9 (28.13%)		(71.88%)	0 (0.00%)	
E. aerogenes [c]					
33	2	7	24	0	0
	9 (27.27%)		(72.73%)	0 (0.00%)	
***E. cloacae* complex** [d]					
98	0	36	57	5	0
	36 (36.73%)		(58.16%)	5 (5.10%)	
E. coli [e]					
136	2	57	71	4	2
	59 (43.38%)		(52.21%	6 (4.41%)	
K. oxytoca [f]					
31	0	14	17	0	0
	14 (45.16%)		(54.84%)	0 (0.00%)	
K. pneumoniae [g]					
128	4	34	84	5	1
	38 (29.69%)		(65.63%)	6 (4.69%)	
M. morganii [h]					
31	4	19	7	0	1
	23 (74.19%)		(22.58%)	1 (3.23%)	
P. rettgeri [i]					
21	4	13	4	0	0
	17 (80.95%)		(19.05%)	0 (0.00%)	
P. stuartii [j]					
21	2	13	6	0	0
	15 (71.43%)		(28.57%)	0 (0.00%)	
S. marcescens [k]					
31	1	19	10	1	0

Total	≥2 dil lower	1 dil lower	Exact	1 dil higher	≥2 dil higher
	20 (64.52%)		(32.26%)	1 (3.23%)	

[a] Percent difference between the higher and lower dilution trends for *C.freundii* is -15.63%; 95% CI (-31.75% to -1.78%)
[b] Percent difference between the higher and lower dilution trends for *C. koseri* is 28.13%; 95% CI (-45.37% to -11.61%
[c] Percent difference between the higher and lower dilution trends for *E. aerogenes* is -27.27%; 95% CI (-44.22% to -11.22%)
[d] Percent difference between the higher and lower dilution trends for *E. cloacae* complex is: -31.63%; 95%CI (-41.93% to -77.26%)
[e] Percent difference between the higher and lower dilution trends for *E. coli* is: -38.97%; 95% CI (-47.70% to -29.57%)
[f] Percent difference between the higher and lower dilution trends for *K. oxytoca* is: -45.16%; 95% CI (-62.23% to -25.73%)
[g] Percent difference between the higher and lower dilution trends for *K. pneumoniae* is: -25%; 95% CI (-33.78% to -16.12%)
[h] Percent difference between the higher and lower dilution trends for *M. morganii* is: -70.97%; 95% CI (-83.36% to -49.23%)
[i] Percent difference between the higher and lower dilution trends for *P. rettgeri* is: -80.95%; 95% CI (-92.33% to -54.91%)
[j] Percent difference between the higher and lower dilution trends for *P. stuartii* is: -71.43%; 95% CI (-86.19% to -45.04%)
[k] Percent difference between the higher and lower dilution trends for *S. marcescens* is: -61.29% 95% CI (-75.90% to -39.45%)

Resistance Markers
Resistance markers for indicated *Enterobacteriaceae* isolates were provided in the submission. They consisted mostly of βeta-lactamses including AmpC (ACT, CMY, DHA), ESBL (CTX-M, TEM, SHV), carbapenemases (KPC, OXA, NDM, VIM, SME). Class A βeta-lactamse (LEN-16) was also included. The study showed that isolates with metallo-βeta-lactamses (NDM, and/or VIM) and OXA carbapenemases were resistant to meropenem/vaborbactam as stated in the drug labeling. The footnote below is added to the performance table in the package insert:

Meropenem/Vaborbactam is not active against bacteria that produce metallo-beta-lactamases, oxacillinases with carbapenemase activity, or porin mutations combined with overexpression of efflux pumps.

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:

FDA susceptibility categories for meropenem/vaborbactam are listed in Table 5.

Table 5: FDA Recognized Interpretive Criteria for Meropenem/Vaborbactam (µg/mL)

	Susceptible (S)	**Intermediate (I)**	**Resistant (R)**
Enterobacteriaceae	≤4/8	8/8	≥16/8

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.