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

A. 510(k) Number:

K183360

B. Purpose for Submission:

To obtain a substantial equivalence determination for Meropenem/Vaborbactam for testing of gram negative bacilli on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

C. Measurand:

Meropenem/Vaborbactam 0.5/8 – 64/8 µg/mL for *Enterobacteriaceae*

D. Type of Test:

Automated quantitative antimicrobial susceptibility test for Meropenem/Vaborbactam.

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK 2 AST-Gram Negative Meropenem/Vaborbactam (≤0.5/8 – ≥64/8 µg/mL)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1645: Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System

2. Classification:

   Class II

3. Product code:

LON – Fully automated short-term incubation cycle antimicrobial susceptibility system
LTW – Susceptibility Test Cards, Antimicrobial
LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   83- Microbiology

H. Intended Use:

1. Intended use(s):

   The VITEK 2 Gram-Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed.

2. Indication(s) for use:

   VITEK 2 AST-Gram Negative Meropenem/Vaborbactam is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of *in vitro* susceptibility to antimicrobial agents. VITEK 2 AST-Gram Negative Meropenem/Vaborbactam is a quantitative test. Meropenem/Vaborbactam has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

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

   In vitro data are available, but clinical significance is unknown:
   Citrobacater freundii
   Citrobacter koseri
   Klebsiella (Enterobacter) aerogenes
   Klebsiella oxytoca
   Morganella morganii
   Proteus mirabilis
   Providencia spp.
   Serratia marcescens

   The VITEK 2 Gram-Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed.

3. Special conditions for use statement(s):

   For Prescription Use Only

   Limitation:
   The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing:

   Meropenem/Vaborbactam: *E. cloacae* complex, *C. freundii, C. koseri, K. aerogenes, K. oxytoca, M. morganii, P. mirabilis, Providencia* spp., *and S. marcescens.*

4. Special instrument requirements:

   VITEK 2 Systems 9.02 (PC version) for all VITEK 2 Systems and VITEK 2 Compact Systems

I. Device Description:

The VITEK 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK 2 AST card contains 64 wells. A control well(s) which contain only nutrient medium is resident on all cards. The remaining wells contain premeasured portions of antimicrobials combined with the nutrient media. The isolate to be tested is diluted to a standardized concentration with 0.45% to 0.50% saline before being used to rehydrate the antimicrobial medium within the card. The VITEK 2 System will automatically dilute the bacterial suspension to prepare an inoculum for susceptibility cards. Then the VITEK 2 will fill, seal and place the card into the incubator/reader. The VITEK 2 Compact has a manual filling, sealing and loading operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time (up to 24 hours for *Streptococcus* species). The analysis program determines when a well demonstrates growth based on attenuation of light measured by an optical scanner. This data is used to determine the minimum inhibitory concentration or "MIC" values for the anti-microbial agent. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antimicrobial contained on the card.

AST-Gram Negative Meropenem/Vaborbactam has the following concentrations in the card: 0.5/8, 2/8, 8/8, and 32/8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The Meropenem/Vaborbactam *Enterobacteriaceae* MIC result range for the VITEK 2 is ≤0.5/8 – ≥64/8 µg/mL .

J. Substantial Equivalence Information:

1. Predicate device name(s):
   VITEK 2 AST-GN Amikacin

2. Predicate 510(k) number(s):
   K172731

3. Comparison with predicate:

Table 1: Comparison with Predicate Device

Similarities		
Item	**Device** **VITEK 2 AST- Gram Negative Meropenem/Vaborbactam** **K183360**	**Predicate** **VITEK 2 AST- Gram Negative Amikacin** **K172731**
Intended Use	VITEK 2 AST-Gram Negative Meropenem/Vaborbactam is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK 2 AST Gram Negative Meropenem/Vaborbactam is a quantitative test. Meropenem/Vaborbactam has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.	VITEK 2 AST Gram Negative Amikacin is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK 2 AST Gram Negative Amikacin is a quantitative test. Amikacin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.
Test Method	Automated quantitative antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems to determine the *in vitro* susceptibility of microorganisms	Same
Inoculum	Standardized saline suspension of test organism	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Analysis Algorithm	Growth pattern analysis	Same
Differences		
Antimicrobial Agent	Meropenem/Vaborbactam	Amikacin

Similarities		
Item	**Device** **VITEK 2 AST- Gram Negative Meropenem/Vaborbactam** **K183360**	**Predicate** **VITEK 2 AST- Gram Negative Amikacin** **K172731**
Antimicrobial Concentrations	0.5/8, 2/8, 8/8, and 32/8	2, 4, 16, and 48

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

- FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)

- CLSI M07-A10, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard- Tenth Edition" Vol. 35 No. 2 (January 2015)

- CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-eighth Edition (January 2018)

L. Test Principle:

The VITEK 2 and VITEK 2 Compact Systems utilize automated growth-based detection using attenuation of light measured by an optical scanner. The optics in the systems uses visible light to directly measure organism growth within each of the 64 micro-wells. Transmittance optics is based on an initial light reading of a well before significant growth has begun. Every 15 minutes throughout the incubation cycle (defined period of time based on the VITEK 2 card), light transmittance readings of each well measures organism growth by the amount of light that is prevented from passing through the well. At the completion of the incubation period, the MIC values and their associated interpretive category results for each antimicrobial on the test card are displayed in an automatically generated report.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   A reproducibility study for the VITEK 2 AST-GN card with Meropenem/Vaborbactam was conducted at three external clinical sites using a panel of ten *Enterobacteriaceae* isolates from indicated species. Testing was performed on three separate days and in triplicate for a total of 270 data points. The isolates tested in the reproducibility study included one isolate each for *E. coli* and *K. aerogenes,* and eight *K. pneumoniae*. Inocula were prepared using both the auto-dilution and manual dilution methods for testing in the VITEK 2 System; inocula were prepared by the manual dilution method only with the VITEK 2 Compact. The mode MIC value was determined and the reproducibility was calculated based on MIC values that fell within +/- one doubling dilution from the mode MIC value. The majority of

data points were on-scale and within ± one doubling dilution agreement as compared to the mode MIC. The reproducibility performance is shown in Table 2.

Table 2: Reproducibility Performance

	VITEK 2		VITEK 2 Compact
	Auto-Dilution	**Manual Dilution**	**Manual Dilution**
Best Case	97.78%	97.41%	96.67%
Worst Case	97.78%	97.41%	96.67%

The combined reproducibility results for all three sites were acceptable.

b. Linearity/assay reportable range:

Not applicable

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

The CLSI recommended QC organisms (*E. coli* ATCC 25922, *E. coli* ATCC 35218, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC BAA-1705, *K. pneumoniae* ATCC BAA-2814, and *K. pneumoniae* ATCC 700603) were tested using both the VITEK 2 card and the reference method at each site. The QC strains were tested a minimum of 20 time per site and inoculated using both the automated dilution and manual dilution for VITEK 2 and using manual dilution for the VITEK 2 Compact.

As shown in Table 3 both the auto-dilution and the manual dilution methods for VITEK 2 and the manual dilution for VITEK 2 Compact gave the expected QC result >95% of the time.

Table 3: Quality Control Summary Results for VITEK 2 (Auto and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Meropenem/ Vaborbactam	**Conc (µg/mL)** [a]	**VITEK 2**				**VITEK 2 Compact Manual Dilution**	
		Auto-Dilution		**Manual-Dilution**			
QC Organism		**Ref.**	**Test**	**Ref.**	**Test**	**Ref.**	**Test**
E. coli ATCC 25922 [b] FDA/CLSI Expected Range 0.008/8 – 0.06/8 (VITEK 2:≤0.5/8)	≤0.004						
	0.008						
	0.016	67		56		56	
	0.03	47		33		33	
	0.06	1		1		1	
	0.125						
	0.25						
	≤0.5 [b]		115		90		90
	1						
	2						
	≥4						

Meropenem/ Vaborbactam	Conc (µg/mL) [a]	VITEK 2				VITEK 2 Compact Manual Dilution	
		Auto-Dilution		Manual-Dilution			
QC Organism		Ref.	Test	Ref.	Test	Ref.	Test
E. coli ATCC 35218 [b, c] FDA/CLSI Expected Range 0.008/8 – 0.06/8 (VITEK 2:≤0.5/8)	≤0.004						
	0.008						
	0.016	67		55		55	
	0.03	48		36		36	
	0.06						
	0.125						
	0.25						
	≤0.5 [b]		115		91		91
	1						
	2						
	≥4						
K. pneumoniae ATCC 700603 [b] FDA/CLSI Expected Range: 0.016 – 0.06 (VITEK 2: ≤0.5/8)	≤0.004						
	0.008						
	0.016	1		1		1	
	0.03	110		86		86	
	0.06	2		2		2	
	0.125	1					
	0.25						
	≤0.5		114		89		89
	1						
	2						
	≥4						
K. pneumoniae ATCC BAA-1705 [b, c] FDA/CLSI Expected Range: 0.016 – 0.06 (VITEK 2: ≤0.5/8)	≤0.004						
	0.008						
	0.016	46		37		37	
	0.03	62		47		47	
	0.06	5		5		5	
	0.125						
	0.25						
	≤0.5		113		89		89
	1						
	2						
	≥4						
K. pneumoniae ATCC BAA-2814 [b, c] FDA/CLSI Expected Range: 0.12 – 0.5 (VITEK 2: ≤0.5/8)	≤0.004						
	0.008						
	0.016						
	0.03						
	0.06						
	0.125	3		2		2	
	0.25	85		64		65	
	≤0.5	22	114	19	88	18	89
	1	3		3		3	

Meropenem/ Vaborbactam	Conc (µg/mL) [a]	VITEK 2				VITEK 2 Compact Manual Dilution	
		Auto-Dilution		Manual-Dilution			
QC Organism		Ref.	Test	Ref.	Test	Ref.	Test
	2	1		1		1	
	≥4				1		
P. aeruginosa ATCC 27853 [b] FDA/CLSI Expected Range: 0.12 – 1 (VITEK 2: ≤0.5/8 – 1/8)	≤0.004						
	0.008						
	0.016						
	0.03						
	0.06						
	0.125						
	0.25	66		49		49	
	≤0.5	39	116	32	92	32	92
	1	11		11		11	
	2						
	≥4						

[a] MIC for meropenem in the presence of a fixed concentration of 8 µg/mL of vaborbactam.

[b] VITEK 2 AST-GN Meropenem/Vaborbactam does not include the full FDA/CLSI recommended QC dilution ranges; include this organism for QC testing.

[c] Refer to current CLSI M100 Table*, Nonfastidious QC for β-Lactam Combination Agents,* for recommendation to ensure that *E. coli* ATCC 35218, *K. pneumoniae* ATCC BAA-1705, and/or *K. pneumoniae* ATCC BAA-2814 have not lost its respective β-lactamase resistance plasmid before conducting QC testing.

The VITEK 2 AST-GN Meropenem/Vaborbactam reporting range is ≤0.5 – ≥64 µg/mL (MIC results: ≤0.5, 1, 2, 4, 8, 16, 32, and ≥64) and does not provide results lower than 0.5 µg/mL. Testing of all six FDA/CLSI recommended QC isolates provided off-scale results with the VITEK 2 card as the acceptable ranges are lower than the lowest concentration on the card (0.5 µg/mL) and a value of ≤0.5 µg/mL is considered an indicator that the quality control test results are acceptable. bioMérieux also includes the FDA/CLSI broth microdilution expected range in the labeling when the VITEK 2 system range is not aligned with that of the FDA/CLSI range. The additional information is acceptable.

The footnote below is added to the QC Table in the package insert recommending testing of *P. aeruginosa* ATCC 27853:

VITEK 2 AST-GN Meropenem/Vaborbactam does not include the full FDA/CLSI recommended QC dilution ranges; include this organism for QC testing.

In addition, *E. coli* ATCC 35218, *K. pneumoniae* ATCC BAA-1705, and/or *K. pneumoniae* ATCC BAA-2814 are recommended to test against meropenem alone to confirm the integrity of the respective QC strain. The footnote below is added to the QC section of the Package Insert of VITEK 2 AST-GN Meropenem/Vaborbactam:

Refer to current CLSI M100 Table, Nonfastidious QC for β-Lactam Combination Agents for recommendation to ensure that E. coli ATCC 35218, K. pneumoniae

ATCC BAA-1705, and/or K. pneumoniae ATCC BAA-2814 have not lost its respective β-lactamase resistance plasmid before conducting QC testing.

Inoculum Density Control
The DensiCHEK Plus was used to standardize the inoculum to a 0.5 McFarland standard. The instrument was standardized daily with all results recorded at each site. Calibration values were within the expected range.

Purity Check
A purity check of all organisms was performed on the dilution tube used to prepare the VITEK 2 card inoculum. Only those cultures that were pure were evaluated in the study.

Growth Failure Rate
A total of 331 isolates were tested at four sites in the clinical study and 118 challenge isolates tested at one external site. All isolates grew.

d. Detection limit:

Not applicable

e. Analytical specificity:

Not applicable

f. Assay cut-off:

Not applicable

2. Comparison studies:

Testing of Meropenem/Vaborbactam on the VITEK 2 AST-Gram Negative card was performed at three external sites and one internal site. Results obtained with the bioMérieux VITEK 2 AST-Gram Negative card with Meropenem/Vaborbactam were compared to results obtained with the CLSI broth microdilution reference panel using direct colony suspension inoculation. Reference panels were incubated at 35° C for 16 to 20 hours. The following concentrations of Meropenem/Vaborbactam are contained in the VITEK 2 AST-GN test card: 0.5/8, 2/8, 8/8, and 32/8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). However, the reporting range is ≤ 0.5 – ≥64 µg/mL for *Enterobacteriaceae*. The reference panel contained two-fold serial dilutions with a range of ≤ 0.004 to ≥256 µg/mL. 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

- Incubation: 35ºC in ambient air for 16 – 20 hours

All test inocula used for the evaluation of VITEK 2 AST-GN Meropenem/Vaborbactam and the reference method were standardized using the DensiCHEK Plus instrument. The cards were inoculated with each test organism by auto-dilution for reading by the VITEK 2 System and by manual dilution for reading on the VITEK 2 and VITEK 2 Compact Systems. Reference broth microdilution panels were inoculated in adherence with CLSI document, M07-A10.

A total of 331 clinical isolates were evaluated at three sites with VITEK 2 AST– Gram Negative cards inoculated by automatic dilution and interpreted using the VITEK 2 instrument. All 331 isolates grew. There were 217 fresh (65.6%) and 114 stock (34.4%) isolates. Of the 331 clinical isolates, 320 (96.7%) were indicated organisms.

A total of 118 challenge organisms were evaluated at one external site. All 118 challenge isolates grew in the study. The challenge set was tested with the auto-dilution and manual dilution options of the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System.

The comparative study (both clinical and challenge) included 438 indicated *Enterobacteriaceae* isolates. They were *E. cloacae* complex (50), *E. coli* (107), *K. pneumoniae* (140), *C. freundii* (8), *C. koseri* (5), *K. aerogenes* (40), *K. oxytoca* (24), *K. pneumoniae ozaenae* (1), *M. morganii* (10), *P. mirabilis* (25), *Providencia* spp. (7), and *S. marcescens* (21).

Overall performance of the indicated isolates is shown in Table 4.1. There were eleven non-indicated *Enterobacteriaceae* isolates tested in the comparative studies. The performance comparison between the indicated isolates and all *Enterobacteriaceae* is shown in Table 4.2 below and no performance difference is observed.

Table 4.1: Performance of Meropenem/Vaborbactam, *Enterobacteriaceae*- Indicated Lists

	EA Total	EA#	EA %	Eval EA Tot	Eval EA#	Eval EA%	CA#	CA %	#R	Min	Maj	Vmj
	Enterobacter cloacae											
Clinical	10	10	100	0	0	0	10	100	0	0	0	0
Challenge	18	16	88.9	2	0	0	17	94.4	1	1	0	0
Combined	28	26	92.9	2	0	0	27	96.4	1	1	0	0
	***E. cloacae* complex**											
Clinical	22	22	100	0	0	0	22	100	0	0	0	0
	E. coli											
Clinical	97	96	99	2	1	50.0	97	100	2	0	0	0
Challenge	10	9	90.0	7	6	85.7	10	100	7	0	0	0
Combined	107	105	98.1	9	7	77.8	107	100	9	0	0	0
	K. pneumoniae											
Clinical	52	52	100	0	0	0	52	100	1	0	0	0
Challenge	77	76	98.7	21	20	95.2	75	97.4	19	2	0	0

	EA Total	EA#	EA %	Eval EA Tot	Eval EA#	Eval EA%	CA#	CA %	#R	Min	Maj	Vmj
Combined	129	128	99.2	21	20	95.2	127	98.4	20	2	0	0
	K. pneum pneumoniae											
Clinical	4	4	100	1	1	100	3	75.0	1	1	0	0
Challenge	**7**	**7**	100	2	2	100	7	100	0	0	0	0
Combined	11	11	100	3	3	100	10	90.9	1	1	0	0
	K. pneumoniae ozaenae											
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
	C. freundii											
Clinical	7	7	100	0	0	0	7	100	0	0	0	0
Challenge	1	1	100	0	0	0	1	100	0	0	0	0
Combined	8	8	100	0	0	0	8	100	0	0	0	0
	C. koseri											
Clinical	5	5	100	0	0	0	5	100	0	0	0	0
	Klebsiella (Enterobacter) aerogenes											
Clinical	39	38	97.4	1	0	0	38	97.4	0	1	0	0
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
Combined	40	39	97.5	2	1	50.0	39	97.5	0	1	0	0
	K. oxytoca											
Clinical	23	23	100	1	1	100	23	100	1	0	0	0
Challenge	1	1	100	1	1	100	1	100	0	0	0	0
Combined	24	24	100	2	2	100	24	100	1	0	0	0
	Morganella morganii											
Clinical	9	9	100	0	0	0	9	100	0	0	0	0
Challenge	1	0	0	1	0	0	0	0	0	1	0	0
Combined	10	9	90.0	1	0	0	9	90.0	0	1	0	0
	P. mirabilis											
Clinical	25	24	96.0	1	0	0	25	100	0	0	0	0
	Providencia* spp. *(P. rettgeri, P. stuartii)											
Clinical (*P. rettgeri*)	3	3	100	0	0	0	3	100	0	0	0	0
Clinical (*P. stuartii*)	4	4	100	0	0	0	4	100	0	0	0	0
	S. marcescens											
Clinical	20	20	100	0	0	0	20	100	0	0	0	0
Challenge	1	1	100	0	0	0	1	100	1	0	0	0
Combined	21	21	100	0	0	0	21	100	1	0	0	0
	Indicated *Enterobacteriaceae*											
Clinical	320	317	99.1	6	3	50.0	318	99.4	5	2	0	0
Challenge	118	113	95.8	36	31	86.1	114	96.6	28	4	0	0
Combined	**438**	**430**	**98.2**	**42**	**34**	**81.0**	**432**	**98.6**	**33**	**6**	**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 VITEK 2 AST-GN 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 VITEK 2 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 VITEK 2 Meropenem/Vaborbactam.

Table 4.2: Performance of Meropenem/Vaborbactam, Comparison Between Indicated Species and All Species within *Enterobacteriaceae*

	EA Total	EA#	EA%	Eval EA Tot	Eval EA#	Eval EA%	CA#	CA %	#R	Min	Maj	Vmj
Indicated Species	438	430	98.2	42	34	81.0	432	98.6	33	6	0	0
All Species within *Enterobacteriaceae*	449	441	98.2	42	34	81.0	443	98.7	33	6	0	0

The performance of the indicated *Enterobacteriaceae* was acceptable at 98.2% EA, 98.6% CA, with no maj or vmj discrepancies. There were eleven *Enterobacteriaceae* isolates (2.4%, 11/449) that were not from the list of indicated species. No performance differences were observed between the indicated species and all organisms within *Enterobacteriaceae*. There were 33 meropenem/vaborbactam resistant isolates tested in the comparative studies. They were *E. coli* and *K. pneumoniae* isolates. A limitation was included in the limitation section of the device labeling:

- The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing:

  Meropenem/Vaborbactam: *E. cloacae* complex, *C. freundii, C. koseri, K. aerogenes, K. oxytoca, M. morganii, P. mirabilis, Providencia* spp., *and S. marcescens.*

To address testing of non-indicated species the sponsor included the following statement in the Precautions section of the device labeling:

> *Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

Challenge Data – Auto and Manual Dilution

A challenge set of 118 *Enterobacteriaceae* isolates was at one external site. The challenge set was tested with both the auto-dilution and manual dilution options of the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System.

Overall performance is shown in Table 5.

Table 5: Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact

Dilution	EA Total	EA #	EA %	Eval EA Total	Eval EA #	Eval EA %	CA #	CA %	#R	Min	Maj	Vmj
VITEK 2												
Auto	118	113	95.8	36	31	86.1	114	96.6	28	4	0	0
Manual	118	112	94.9	35	29	82.9	114	96.6	28	4	1	0
VITEK 2 Compact												
Manual	118	111	94.1	38	31	81.6	115	97.5	28	3	0	0

The performance of the Meropenem/Vaborbactam test with the challenge isolates on VITEK 2 and VITEK 2 Compact Systems was acceptable.

MIC Trends

An analysis of trending was conducted using the combined clinical and challenge data for each organism group. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Trending results for overall indicated species and all species within *Enterobacteriaceae* are shown in Table 6 and no trending was observed. In the analysis, results were stratified by species to determine if species-related trends were observed. A difference of ≥30 between the percentage of a species with higher vs. lower readings and for which the confidence interval was determined to be statistically significant was considered to show evidence of trending. No species demonstrated significant trending.

Table 6: Trending Analysis of *Enterobacteriacea* (Clinical + Challenge)

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
Indicated Species	43	18 (41.86%)	13 (30.23%)	12 (27.91%)	-13.95% (-32.50% - 6.05%)	No
All Species within *Enterobacteriaceae*	44	18 (41.86%)	13 (30.23%)	12 (27.91%)	-13.95% (-32.50% -6.05%)	No

Enzyme Group Characterization/Resistance Markers Information

Resistance markers for indicated *Enterobacteriaceae* isolates were provided in the submission. They consisted mostly of βeta-lactamases including AmpC (ACT/MIR, hyper AmpC), ESBL/OSBL (CTX-M, TEM, SHV), carbapenemases (KPC, OXA, NDM, VIM), porin mutation (OMPC, OMPK). The study showed that isolates with metallo-βeta-lactamases (NDM, and/or VIM) 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:

> The following enzyme group characterization was not available for *Enterobacteriaceae* at the time of comparative teting, and therefore the performance of the AST-GN Meropenem/Vaborbactam is unknown: SME, CMY, ACT, and porin mutations combined with overexpression of efflux pumps.

a. Method comparison with predicate device:

Not applicable

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:

Table 7: Interpretive Criteria for Meropenem/Vaborbactam (FDA STIC Webpage and CLSI M100)

Organism	MIC (µg/mL)		
	Susceptible	**Intermediate**	**Resistant**
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.