510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K183127

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Meropenem/Vaborbactam to the MicroScan Dried Gram-Negative MIC/Combo Panels with Meropenenem/Vaborbactam (0.03/8 – 64/8 µg/mL).

C. Measurand:

Meropenenem/Vaborbactam in the dilution range of 0.03/8 – 64/8 µg/mL.

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST)

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

MicroScan Dried Gram-Negative MIC/Combo Panels with Meropenenem/Vaborbactam (0.03/8 – 64/8 µg/mL).

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product codes:

   LTT – Panels, Test, Susceptibility, Antimicrobial
   JWY – Manual Antimicrobial Susceptibility Test Systems
   LRG – Instrument for Auto Reader and Interpretation of Overnight Susceptibility

Systems
LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended use(s):

   For use with MicroScan Dried Gram Negative MIC/Combo Panels and Dried Gram Negative Breakpoint Combo panels. MicroScan panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of aerobic and facultatively anaerobic gram-negative bacilli.

2. Indication(s) for use:

   The MicroScan Dried Gram-Negative MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram-negative bacilli. After inoculation, panels are incubated for 16 – 20 hours at 35°C ± 1°C in a non-CO_2 incubator, and read either visually or with MicroScan instrumentation, according to the package insert.

   This particular submission is for the addition of the antimicrobial meropenem/vaborbactam at concentrations of 0.03/8 to 64/8 µg/mL to the test panel.

   The gram-negative organisms which may be used for meropenem/vaborbactam susceptibility testing in this panel are as follows:

   Meropenem/vaborbactam has been shown to be active both clinically and in vitro against the gram negative bacteria listed below according to the FDA drug approved label:

   - *Enterobacter cloacae complex*
   - *Escherichia coli*
   - *Klebsiella pneumoniae*

   Meropenem/vaborbactam has been shown to be active in vitro only against the gram-negative bacteria listed below according to the FDA drug approved label:

   - *Citrobacter freundii*
   - *Citrobacter koseri*
   - *Enterobacter aerogenes*
   - *Klebsiella oxytoca*
   - *Morganella morganii,*

- *Proteus mirabilis*
- *Providencia spp*
- *Serratia marcescens*

3. Special conditions for use statement(s):

   For Prescription use only.

   The following limitations are included in the labeling:

   - "*Performance of meropenem/vaborbactam when testing Morganella morganii using the Prompt Inoculation system with the autoSCAN-4 or manual read methods were outside of essential agreement compared to the reference method and should be tested using the turbidity inoculation method*."

   - "*Elevated MICs with beta-lactam antimicrobials (e.g. aztreonam, ceftazidime/avibactam, Ceftolozane/tazobactam, meropenem/vaborbactam) may be observed if panels are over-inoculated with microorganisms such as Pseudomonas aeruginosa, Serratia spp., Proteus spp., Morganella spp., and Providencia spp. Inoculum concentration is critical with these antimicrobials as their mechanism of action involves disruption of bacterial cell wall synthesis. The user should pay careful attention to inoculum preparation, especially with manual methods that are technique dependent such as the Prompt system or inoculum prepared without the aid of a photometric device*".

   - "*The ability of the MicroScan Dried Negative Panels to detect resistance to meropenem/vaborbactam is unknown with C. koseri, E. aerogenes, K. oxytoca, M. morganii, P. mirabilis, Providencia species and S. marcescens because resistant strains were not available at the time of comparative testing. If such isolates are observed, they should be tested on an alternate method and /or submitted to a reference lab*".

   - "*Meropenem/vaborbactam is not active against bacteria that produce metallo-beta lactamases or oxacillinases with carbapenemase activity".*

4. Special instrument requirements:

   MicroScan panels can be read either manually or automatically on the WalkAway or autoSCAN-4 instrument systems.

I. Device Description:

The MicroScan Dried Gram-Negative MIC/Combo panel with meropenem/vaborbactam is used to determine the quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram negative bacilli. After inoculation, panels are incubated for 16-20 hours at 35°C ± 1°C in a

non-CO_2 incubator and read either visually or with MicroScan instrumentation according to the package insert.

Inoculation methods: Prompt Inoculation System (primary inoculation method) and Turbidity (alternate inoculation method).

Read methods: MicroScan WalkAway System (primary read method) and Manual, MicroScan autoSCAN-4 (alternate read methods).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   MicroScan Dried Gram Negative MIC/Combo Panels – ceftazidime/avibactam

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

   K172337

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	**Device (K183127)**	**Predicate (K172337)**
Device	MicroScan Dried Gram Negative MIC/Combo Panels – meropenem/vaborbactam	MicroScan Dried Gram Negative MIC/Combo Panels – ceftazidime/avibactam (K172337)
Technology	Overnight microdilution MIC susceptibility	Same
Result Reported	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Same
Read Methods	Manual and automated	Same
Inoculation Methods	Turbidity and Prompt	Same
Instrumentation	WalkAway or autoSCAN-4 Instrument systems	Same
Specimen	Isolated colonies from cultures	Same
Incubation Temperature	35°C ± 1°C	Same
Incubation Atmosphere	Aerobic	Same
Incubation Time	16-20 hours	Same
Differences		
Item	Device	Predicate
Intended Use	Determination of susceptibility to meropenem/vaborbactam with gram-negative bacteria	Determination of susceptibility to ceftazidime/avibactam with gram-negative bacteria

Similarities		
Item	**Device (K183127)**	**Predicate (K172337)**
Antimicrobial Agent	Dried Meropenem/vaborbactam 0.03/8– 64/8 µg/mL	Dried Ceftazidime/avibactam 0.25/4 – 64/4 µg/mL

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

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA
2. CLSI M07-11th Edition. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, January, 2018.
3. CLSI M100-S28. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Eight Informational Supplement, January 2018.

L. Test Principle:

The antimicrobial susceptibility tests are dehydrated miniaturizations of the broth dilution susceptibility test. Various antimicrobial agents are diluted in Mueller Hinton broth supplemented with calcium and magnesium to concentrations spanning the range of clinical interest. Breakpoint Combo panels use concentrations equivalent to the categorical breakpoints of FDA and/or CLSI. After inoculation and rehydration with a standardized suspension of organism and incubation at 35°C for a minimum of 16 hours, the minimum inhibitory concentration (MIC) for the test organism is determined by observing the lowest antimicrobial concentration showing inhibition of growth.

M. Performance Characteristics:

1. Analytical performance:

   a. Precision/Reproducibility:

   A reproducibility study was conducted at three external sites using 14 gram negative strains that were consistent with the intended use. The range of Meropenem/vaborbactam dilutions tested was 0.03/8 to 64/8 µg/mL. Isolates were tested in triplicate over three days (total of 27 replicates per strain). The isolates tested in the reproducibility study included C. *freundii* (one isolate), *E. aerogenes* (one isolate), *E. cloacae* (one isolate), *E. coli* (three isolates), *K. oxytoca* (one isolate), *K. pneumoniae* (three isolates), *P. aeruginosa* (two isolates), *P. mirabilis* (one isolate), *S. marcescens* (one isolate). Inocula were prepared using both the turbidity and Prompt inoculum methods and results were read manually and with the WalkAway (WA) and autoSCAN-4 (AS4) instruments.

   The majority of data points were on-scale and within ± one doubling dilution

agreement as compared to the mode MIC (Table 2). One data point was off-scale using the Prompt inoculation method and the WA read method, three data points were off-scale using the Prompt inoculation method and the AS4 read method and four data points were off-scale using the Turbidity inoculation method and the AS4 reading method. As shown in Table 2, the data was analyzed taking into consideration best case and worst case scenarios as described in the Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems:

Table 2. Reproducibility with all Inoculation and Read Methods (All Sites).

Read Method		Prompt Inoculation	Turbidity Inoculation
WalkAway	Best Case	363/378 (96.0%)	371/378 (98.1%)
	Worst Case	363/378 (96.0%)	371/378 (98.1%)
autoSCAN-4	Best Case	362/378 (95.8%)	371/378 (98.1%)
	Worst Case	359/378 (95.0%)	367/378 (97.1%)
Manual	Best Case	366/378 (96.8%)	367/378 (97.1%)
	Worst Case	366/378 (96.8%)	367/378 (97.1%)

The reproducibility results were acceptable at ≥ 95%.

b. *Linearity/assay reportable range:*

Not Applicable

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

Inoculum Density Check. A spectrophotometric device, the MicroScan Turbidity Meter was used to ensure quality control of the turbidity inoculum method. The turbidity inocula were prepared using the MicroScan Turbidity Meter with a reading of 0.08 ± 0.02 (equivalent to a 0.5 McFarland barium sulfate turbidity standard). The digital reading was recorded each day of use at each clinical trial site.

Organism density data was also collected during the Reproducibility phase of the study for suspensions prepared using the Prompt inoculum preparation method. Colony counts were performed weekly using the quality control strain *E. coli* ATCC 25922. Colony counts were also done once at each site for each reproducibility isolate. All results were acceptable.

Purity Check. Purity check plates were performed on all isolates tested during the clinical study for meropenem/vaborbactam. If a purity plate indicates mixed culture, the isolate was retested.

Growth Failure Rate. During the clinical trial, there were no growth failures with both the MicroScan panel and the CLSI frozen reference method with Meropenem/vaborbactam.

Quality Control Testing. The CLSI and FDA recommended QC organisms (*E. coli*

ATCC 25922, *P. aeruginosa* ATCC 27853, *E. coli* ATCC35218 and *K. pneumoniae* ATCC 700603) were tested using the meropenem/vaborbactam dilution range of 0.03/8 – 64/8 µg/mL for both the device and reference panel. Testing was performed with both Turbidity and Prompt inoculation methods and all read methods (manual, WalkAway instrument and autoSCAN-4 instrument). The reference panel was inoculated using the turbidity inoculation method only. Results are outlined in Table 3.

Table 3. Quality Control Results with the Extended Dilution Range for all Sites

Organism	Conc. (µg/mL)	Ref	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
E. coli[1] ATCC 25922 **Expected Range 0.008/8 – 0.06/8 µg/mL**	≤0.03*	121	102	121	119	120	119	120
	0.06		19		2			
	0.12							
	0.25						1	1
	0.5					1		
	1							
	2							
	4							
	8							
	16							
	32							
	64							
	>64							
***P. aeruginosa* ATCC 27853 Expected Range 0.125/8 -1/8 µg/mL**	≤0.03							
	0.06							
	0.12		2			3		3
	0.25	53	79	75	80	79	69	73
	0.5	55	31	32	32	31	42	36
	1	13	6	10	6	8	10	9
	2		2	2	2			
	4							
	8							
	16							
	32							
	64			1	1			
	>64		1					
E. coli[1] ATCC 35218 **Expected Range 0.008/8 – 0.06/8**	≤0.03*	118	117	116	117	118	117	118
	0.06							
	0.12							
	0.25							
	0.5							
	1							
	2							
	4							
	8							
	16							

Organism	Conc. (µg/mL)	Ref	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
	32							
	64							
	>64		1	1	1			
K. pneumoniae[1] ATCC 700603 **Expected range 0.016/8-0.06/8**	≤0.03*	112	11	10	14	2	1	1
	0.06	5	101	102	98	110	111	111
	0.12		1	1	1	3	3	3
	0.25		1	1	1	2	2	2
	0.5	1	3	3	3			
	1							
	2							
	4							
	8							
	16		1	1	1			
	32							
	64							
	>64							
K. pneumoniae[2] **ATCC BAA-1705** **0.008/8-0.064/8**	≤0.03*	114	91	105	104	97	94	96
	0.06	3	25	12	12	14	17	15
	0.12				1	4	4	4
	0.25					1	2	1
	0.5							1
	1					1		
	2							
	4							
	8							
	16							
	32							
	64							
	>64							

*The lowest end point of the MicroScan Meropenem/Vaborbactam MIC range is ≤0.03 µg/mL. Obtaining this value was considered as an indicator that the quality control test results were acceptable.

[1]*E. coli* ATCC 25922, *E. coli* ATCC 35218, and *K. pneumoniae* ATCC 700603 are not required for routine testing.

[2]*K. pneumoniae* ATCC BAA-1705 is recommended for routine QC with Meropenem/Vaborbactam. The QC range for *K. pneumoniae* ATCC BAA-1705 is ≤0.03/8-0.06/8 µg/mL (Table 3a).

Because of the meropenem/vaborbactam dilution range of 0.03/8 – 64/8 µg/mL, all MIC values for the QC strains tested were off-scale, except for *P. aeruginosa* ATCC 27853. Therefore, only *P. aeruginosa* ATCC 27853 is recommended for QC testing of meropenem/vaborbactam. In addition, *K. pneumoniae* BAA-1705 is recommended for routine QC with meropenem/vaborbactam and with meropenem alone. The strains included in the Quality Control section of the MicroScan Dried Gram Negative Procedural Manual are shown in Table 3a.

Table 3a. Recommended QC strains for Meropenem/Vaborbactam

Antimicrobial Agent	Organism	ATCC #	Range (µg/mL)
Meropenem/Vaborbactam	*P. aeruginosa*	27853	0.12/8-1/8
	*K. pneumoniae**	BAA-1705	≤0.03/8-0.06/8

*to ensure that the plasmid encoding β-lactamase has not been lost, this strain was tested using a single β-lactam agent (meropenem) as instructed in CLSI M100, 28th ed. QC performance of meropenem on the frozen reference panel confirmed the integrity of this QC strain to reliably QC meropenem/vaborbactam at all sites.

Quality control results of all QC organisms tested met the acceptance criteria of > 95% agreement with the expected value for all inoculation and read methods and demonstrated that the system could produce the expected quality control results.

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 results obtained with the MicroScan Dried Gram-Negative MIC/Combo Panel with meropenem/vaborbactam were compared to results obtained using a frozen broth microdilution reference panel at three testing sites in the U.S.

The reference panel was prepared according to CLSI M07-A10 guidelines except for the use of Pluronic-F in the inoculum water for the reference panel. A validation study was performed to demonstrate equivalence between reference panels inoculated with organisms suspended in water supplemented with Pluronic-F and reference panels inoculated with autoclaved distilled water without Pluronic-F. The essential agreement (EA) of MIC values obtained using Pluronic-F as the diluent as compared to MIC values obtained using autoclaved distilled water as the diluent was 100% and the categorical agreement (CA) was 92.9%.

The *Enterobacteriaceae* clinical data was collected on a dried test panel which included twelve dilutions of meropenem/vaborbactam (0.03/8-64/8 µg/mL). The data analysis was performed by comparing test panel results to the reference results.

For each organism tested, MicroScan panels and reference panels were inoculated using the same standardized suspension further diluted into 25 mL of water with either Pluronic-D (for the MicroScan dried panels) or Pluronic-F (for the frozen reference panels). Panels were inoculated using both the Prompt System and by the Turbidity method; MicroScan panels were read using the WalkAway, the autoSCAN4 and Manual Read. The reference panels were read manually. Performance was

evaluated using FDA breakpoints for Meropenem/vaborbactam, and results were analyzed based on the guidelines provided in the AST Class II Special Controls Guidance Document. The primary read has been identified as the WalkAway system with the prompt inoculation system. The clinical data are also presented on the two secondary read methods collected at the three sites, which includes MicroScan and autoSCAN-4 instruments and manual reads with both Prompt and turbidity inoculation methods.

Clinical Study:
Clinical testing was performed at three US sites. A total of 560 *Enterobacteriaceae* clinical isolates were tested including *C. freundii* (63 isolates), *C. koseri* (57 isolates), *E. aerogenes* (55 isolates), *E. cloacae* complex (67 isolates) *E. coli* (64 isolates), *K. oxytoca* (49 isolates), *K. pneumoniae* (59 isolates), *M. morganii* (29 isolates), *P. mirabilis* (32 isolates), Providencia species (51 isolates) and *S. marcescens* (34 isolates). Of the 560 clinical isolates, 358 (69.10%) were fresh isolates,136 (24.3%) were recent isolates and 66 (11.8%) were stock isolates.

Challenge Study:
Challenge testing was performed at one internal site. A total of 95 challenge isolates of *Enterobacteriaceae* were evaluated. The *Enterobacteriaceae* isolates included *C. freundii* (4 isolates), *C. koseri* (3 isolates), *E. aerogenes* (5 isolates), *E. cloacae* complex (13 isolates), *E. coli* (10 isolates), *K. oxytoca* (4), *K. pneumoniae* (30 isolates), *M. morganii* (4 isolates),,*P. mirabilis* (5 isolates), *Providencia* species (11 isolates), and *S. marcescens* (6 isolates).

The performance of the 655 clinical and challenge isolates is summarized in Tables 3 and 4.

Table 4. Performance of MicroScan Dried Gram-Negative Panels with Meropenem/vaborbactam with *Enterobacteriaceae*, Prompt Inoculation Method, All Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	Min (%)	Maj (%)	Vmj (%)
WalkAway													
Clinical	560	553	98.8	145	138	95.2	560	100	1	559	0 (0%)	0 (0%)	0 (0%)
Challenge	95	91	95.8	72	70	97.2	89	93.7	30	60	6 (6.3%)	0 (0%)	0 (0%)
Combined	655	644	**98.3**	217	208	95.9	649	**99.1**	31	619	6 (0.9%)	0 (0%)	0 (0%)
autoSCAN-4													
Clinical	560	549	98	139	129	92.8	560	100	1	559	0 (0%)	0 (0%)	0 (0%)
Challenge	95	88	92.6	72	68	94.4	89	93.7	30	60	6 (6.3%)	0 (0%)	0 (0%)
Combined	655	637	**97.3**	211	197	93.4	649	**99.1**	31	619	6 (0.9%)	0 (0%)	0 (0%)
Manual													

Clinical	560	540	96.4	146	129	88.4	560	100	1	559	0 (0%)	0 (0%)	0 (0%)
Challenge	95	92	96.8	72	71	98.6	89	93.7	30	60	6 (6.3%)	0 (0%)	0 (0%)
Combined	655	632	**96.5**	218	200	91.7	649	**99.1**	31	619	6 (0.9%)	0 (0%)	0 (0%)

Table 5. Performance of MicroScan Dried Gram-Negative Panels with Meropenem/vaborbactam with *Enterobacteriaceae*, Turbidity Inoculation Method, All Read Methods

	Tot	**No. EA**	**EA %**	**Eval EA Tot**	**No. Eval EA**	**Eval EA %**	**No. CA**	**CA %**	**No. R**	**No. S**	**min**	**maj**	**vmj**
WalkAway													
Clinical	560	555	99.1	145	140	96.6	560	100	1	559	0 (0%)	0 (0%)	0 (0%)
Challenge	95	88	92.6	71	65	91.5	85	89.5	30	60	9 (6.5%)	0 (0%)	1 (3.3%)
Combined	655	643	**98.2**	216	205	94.9	645	**98.5**	31	619	9 (1.4%)	0 (0%)	1 (3.2%)
autoSCAN-4													
Clinical	560	554	98.9	138	132	95.7	560	100	1	559	0 (0%)	0 (0%)	0 (0%)
Challenge	95	87	91.6	72	65	90.3	85	89.5	30	60	9 (9.5%)	0 (0%)	1 (3.3%)
Combined	655	641	**97.9**	210	197	93.8	645	**98.5**	31	619	9 (1.4%)	0 (0%)	1 (3.2%)
Manual Read													
Clinical	560	553	98.8	146	140	95.9	560	100	1	559	0 (0%)	0 (0%)	0 (0%)
Challenge	95	88	92.6	72	66	91.7	85	89.5	30	60	9 (9.5%)	0 (0%)	1(3.3%)
Combined	655	641	**97.9**	218	206	94.5	645	**98.5**	31	619	9 (1.4%)	0 (0%)	1 (3.2%)

EA – Essential Agreement (+/- 2 dilutions)
CA – Category Agreement
EVAL – Evaluable isolates
R or NS – Resistant or non-susceptible isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

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

<u>Overall Performance</u>:
The overall essential agreement and category agreement of the MicroSCAN Meropenem/Vaborbactam for all *Enterobacteriaceae* is acceptable at ≥90.0 % for both inoculation methods across all read methods (Tables 4 and 5). The essential agreement of evaluable results was also acceptable with both the prompt and the turbidity inoculation methods across all read methods.

With the Prompt inoculation method across all reads, there was no very major or major discrepancies; (Table 4). The minor discrepancy rate was 0.9% (6/655).

The high very major error rate of 3.3% observed with the turbidity inoculation method across all read methods (Table 5) was attributed to *Citrobacter freundii* strains which had one of two challenge resistant isolates false susceptible result with an MIC of 4µg/mL with test panel and an MIC of 16µg/mL by the reference method. The following footnote was added to the Procedural Manual:

> *"One of the two resistant Citrobacter freundii strains had discrepant results compared to the reference method when using the turbidity inoculation method across all read methods".*

Since the number the number of resistant isolates tested during the comparative studies was low (31), 25 additional resistant isolates were evaluated during verification on all read and inoculation methods. The combined data of 56 resistant isolates had no additional very major errors. The expansion of the resistant isolates pool resulted in a very major error rate less than 2% which is acceptable.

Morganella morganii was observed to have low essential agreement with Prompt inoculation method when read on the autoSCAN-4 instrument (84.8%) and manually (72.7%), whereas categorical agreement was 100%. However, the performance of this organism was acceptable when read by the WalkAway with an essential agreement of 93.9%. The following limitation are included in the procedural manual:

> "*Performance of meropenem/vaborbactam when testing Morganella morganii using the Prompt Inoculation system with the autoSCAN-4 or manual read methods were outside of essential agreement compared to the reference method and should be tested using the turbidity inoculation method*".
>
> "*Elevated MICs with beta-lactam antimicrobials (e.g. aztreonam, ceftazidime/avibactam, Ceftolozane/tazobactam, meropenem/vaborbactam) may be observed if panels are over-inoculated with microorganisms such as Pseudomonas aeruginosa, Serratia spp., Proteus spp., Morganella spp., and Providencia spp. Inoculum concentration is critical with these antimicrobials as their mechanism of action involves disruption of bacterial cell wall synthesis. The user should pay careful attention to inoculum preparation, especially with manual methods that are technique dependent as the Prompt system or inoculum prepared without the aid of a photometric device*".

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

"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".

Resistant Organisms:
A total of 31 resistant isolates were identified out of 655 organisms tested (4.7%) in the combined challenge and clinical study of with Meropenem/vaborbactam However, the following indicated organisms had no resistant isolates available during comparative testing: *Citrobacter koseri, Enterobacter aerogenes, Klebsiella oxytoca, Morganella morganii, Proteus mirabilis, Providencia species and Serratia marcescens.* This was addressed by adding the following limitation in the labeling:

> "*The ability of the MicroScan Dried Negative Panels to detect resistance to meropenem/vaborbactam is unknown with C. koseri, E. aerogenes, K. oxytoca, M. morganii, P. mirabilis, Providencia species and S. marcescens because resistant strains were not available at the time of comparative testing. If such isolates are observed, they should be tested on an alternate method and /or submitted to a reference lab*".

Trending:
An analysis of trending was conducted using the combined clinical and challenge data for *Enterobacteriaceae* and for each claimed species within the *Enterobacteriaceae* group with meropenem/vaborbactam 0.03/8-64/8 µg/mL for both inoculation methods (Prompt and Turbidity).

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 for both systems are on-scale or not. A difference of ≥30% between the percentage of isolates with higher versus lower readings compared to the reference method was considered evidence of significant trending. Trending that provides higher or lower MIC values compared to the reference is addressed in labeling.

The analysis for trending takes into account only results that are evaluable for trending. Results that cannot be evaluated because it is unclear if they are at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not taken into account in the trending analysis.

The analysis for which significant high trending was observed is outlined in Tables 6 and 7 below. Table 6 demonstrates the results for Prompt inoculation method by reading method for each species and by manual reading for all *Enterobacteriaceae*. Table 7 demonstrates the results for Turbidity inoculation method by reading method for *Providencia* species.

Table 6. Trending Analysis Stratified by Species (Clinical and Challenge Combined) using the Prompt Inoculation Method

Total Evaluable For Trending	≥2 dil lower	1 dil lower	Exact	1 dil higher	≥2 dil higher
Morganella morganii					
WA [a]					
32	0	1	18	11	2
	1 (3.13%)			13 (40.63%)	
Manually [b]					
32	0	0	10	13	9
	0 (0%)			22 (68.75%)	
Providencia spp					
WA [c]					
60	0	2	26	26	6
	2 (3.33%)			32 (53.33%)	
AS4 [d]					
58	0	3	25	24	6
	3 (5.17%)			30 (51.72%)	
Manual [e]					
58	0	2	18	34	4
	2 (3.45%)			38 (65.52%)	
Proteus mirabilis					
Manual [f]					
37	0	5	15	13	4
	5 (13.51%)			17 (45.95%)	
***Enterobacter cloacae* complex**					
WA [g]					
23	0	0	10	2	11
	0 (0%)			13 (56.52%)	
AS4 [h]					
22	0	0	10	10	2
	0 (0%)			12 (54.55%)	
Manual[i]					
25	0	0	10	13	2
	0 (0%)			15 (60%)	
Enterobacteriaceae[j]					
Manual					
272	0	21	101	127	23
	21 (7.72%)			150 (55.15%)	

[a] Percent difference between the higher and lower dilution trends is: -37.50%
[b] Percent difference between the higher and lower dilution trends is: -68.75%
[c] Percent difference between the higher and lower dilution trends is: -50%
[d] Percent difference between the higher and lower dilution trends is: -46.55%
[e] Percent difference between the higher and lower dilution trends is: -62.07%
[f] Percent difference between the higher and lower dilution trends is: -32.43%
[g] Percent difference between the higher and lower dilution trends is: -56.52%
[h] Percent difference between the higher and lower dilution trends is: -54.55%
[i] Percent difference between the higher and lower dilution trends is: -60%%
[j] Percent difference between the higher and lower dilutions trends is: -47.43%

Table 7. Trending Analysis for *Providencia* spp (Clinical and Challenge Combined) using the Turbidity Inoculation Method

Total Evaluable For Trending	≥2 dil lower	1 dil lower	Exact	1 dil higher	≥2 dil higher
Providencia spp					
AS4[a]					
56	0	2	34	20	0
	2 (3.57%)			20 (35.71%)	
Manual[b]					
57	0	0	35	21	1
	0 (0%)			22 (38.60%)	

[a]Percent difference between the higher and lower dilution trends for AS4 is: -32.14%
[b]Percent difference between the higher and lower dilution trends for Manual is: -38.60%

Based on the above results, the following footnotes were added to the meropenem/vaborbactam Procedural Manual to address the observed trending:

> *"Meropenem/vaborbactam MIC values tended to be one or more doubling dilution higher when compared to the reference broth microdilution method for P. mirabilis., Providencia spp., Enterobacter cloacae complex and Morganella morganii with the WalkAway, autoSCAN-4 and manual reads when using the Prompt Inoculation system. Additionally, Meropenem/vaborbactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing Enterobacteriaceae when using the Prompt Inoculation system and the manual read compared to the CLSI reference broth method"*
>
> *"Meropenem/vaborbactam MIC values tended to be in exact agreement or at least one doubling dilution higher when compared to the reference broth microdilution for Providencia spp. with autoSCAN-4 and manual reads when using the turbidity Inoculation method".*

Resistance Mechanisms:

The meropenem/vaborbactam approved drug label indicates activity against specific resistance mechanisms. Therefore, resistance mechanisms for indicated *Enterobacteriaceae* isolates were tested in the challenge phase and provided in the submission. They consisted mostly of βeta-lactamases and Extended-spectrum Beta-lactamases (Table 7).

Table 8. Summary of *Enterobacteriaceae* Beta-Lactamases and Extended-spectrum Beta-Lactamases Resistance Mechanisms Tested

Resistance Mechanism	Number Tested*
KPC	18
SME	5
TEM	28
SHV	29
CTX-M	26
ACT	6
OXA	23

*Isolates tested may harbor one or more resistance mechanism

Based on the resistance mechanism information included in the approved drug label for meropenem/vaborbactam, the following limitation is added to the procedural manual:

> *"Meropenem/Vaborbactam is not active against bacteria that produce metallo-beta-lactamases, oxacillinases with carbapenemase activity".*

b. Matrix comparison:

N/A

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data:

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Table 9. FDA Recognized Interpretive Criteria for Meropenem/Vaborbactam (µg/mL)

Organism	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.