510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K173523

B. Purpose for Submission:

Addition of Meropenem/vaborbactam to the BD Phoenix Gram negative ID/AST and AST only Phoenix panels

C. Measurand:

Meropenem/vaborbactam 0.125/8-32/8 µg/mL

D. Type of Test:

Antimicrobial Susceptibility Test (Quantitative) colorimetric, oxidation-reduction, growth based

E. Applicant:

Becton, Dickinson and Company

F. Proprietary and Established Names:

BD Phoenix Automated Microbiology System - GN Meropenem-vaborbactam (0.125/8-32/8 µg/mL)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1645 Short-Term Antimicrobial Susceptibility Test System

2. Classification:

   Class II

3. Product codes:

   LON – System, Test, Automated, Antimicrobial Susceptibility, Short Incubation

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended use(s):

   The BD Phoenix Automated Microbiology System is intended for the *in vitro* rapid identification (ID) and quantitative determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of Gram Negative aerobic and facultative anaerobic bacteria belonging to the family *Enterobacteriaceae* and non-*Enterobacteriaceae.*

2. Indication(s) for use:

   The BD Phoenix™ Automated Microbiology System is intended for *in vitro* quantitative determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of most Gram-negative aerobic and facultative anaerobic bacteria isolates from pure culture for *Enterobacteriaceae* and Non-*Enterobacteriaceae* and most Gram-positive bacteria isolates from pure culture belonging to the genera *Staphylococcus*, *Enterococcus* and *Streptococcus*.

   Meropenem-vaborbactam has been shown to be active in vitro against most strains of microorganisms listed below, as described in the FDA-approved package insert for this antimicrobial agent.

   Active *in vitro* and in Clinical Infections Against:
   Enterobacter cloacae species complex
   Escherichia coli
   Klebsiella pneumoniae

   Active *in vitro* but clinical significance is unknown
   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 information is included as a limitation in labeling:

   - *The ability of the BD Phoenix AST system to detect resistance to meropenem/vaborbactam in the following species is unknown because resistant strains were not available or insufficient at the time of comparative testing: C. freundii, C. koseri, E. cloacae, E. aerogenes, E. coli, K. oxytoca, M. morganii, P. mirabilis, P. stuartii, and S. marcescens.*

   - *Due to a small number of Enterobacteriaceae on-scale isolates available for comparative testing, there is limited data regarding performance of the BD Phoenix Gram-negative for meropenem/vaborbactam particularly around the breakpoints. Therefore, though rare, isolates with MIC values of 4/8, 8/8 and 16/8 µg/mL should be confirmed with an alternate method.*

4. Special instrument requirements:

   BD Phoenix Instrument and software (V5.83A or higher)
   PhoenixSpec Nephelometer
   BD Phoenix AP instrument

I. Device Description:

This submission is for a single drug in the gram negative ID/AST or AST only panel. The ID portion of the ID/AST combination panel was not subject for review in this submission.

The Phoenix AST method is a broth based microdilution test. The Phoenix panel is a sealed and self-inoculating molded polystyrene tray, with 136 micro-wells containing dried reagents. The ID/AST combination panel includes an ID side (51 wells) with dried substrates for bacterial identification and an AST side (85 wells). The AST panel contains a wide range of two-fold doubling dilution concentrations of antimicrobial agents and growth and fluorescent controls at appropriate well locations. The AST panel does not include wells for isolate identification.

The Phoenix System utilizes a redox indicator for the detection of organism growth in the presence of an antimicrobial agent. The organism to be tested must be a pure culture and be preliminarily identified as Gram-positive or Gram-negative. Colonies are then suspended in ID broth, and equated to a 0.5 McFarland suspension using a nephelometer device. A further dilution is made into AST broth (a cation-adjusted formulation of Mueller-Hinton broth containing 0.010% Tween 80), to which the redox-buffered oxidation-reduction AST indicator solution is added producing a blue color in the wells. The concentration of organisms in the final AST broth suspension is approximately 5 X 10^5 CFU/mL.

The Phoenix AST Broth is poured into the inoculation port of the AST panel and the inoculum flows into the panel, filling panel wells. Polyethylene caps are applied to seal the inoculation ports. An air admittance port is located in the panel lid to ensure adequate oxygen tension in the panel for the duration of the test. Inoculated panels are barcode scanned and loaded into the BD Phoenix Automated Microbiology System instrument where panels are continuously incubated at 35^{o} C ± 1^{o} C.

Continuous measurements of changes to the indicator as well as bacterial turbidity are used in the determination of bacterial growth. The instrument takes readings every 20 minutes. Organisms growing in the presence of a given antimicrobial agent reduce the indicator (changing it to a pink color). This signals organism growth and resistance to that antimicrobial agent. Organisms killed or inhibited by the antimicrobial agent do not cause reduction of the indicator and therefore do not produce a color change. The Phoenix instrument reads and records the results of the antimicrobial tests contained in the panel and interprets the reactions (based on the organism identification) to give a minimal inhibitory concentration (MIC) value and category interpretations (susceptible, intermediate, resistant or not susceptible). AST results are available within 4 to 16 hours. This is an autoread result; no manual readings are possible with this system.

Additional comments concerning specific organism/antimicrobial combinations is provided from the software-driven "EXPERT" system, using rules derived from CLSI documentation.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   BD Phoenix Automated Microbiology System with Tigecycline (0.25-16 µg/mL)

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

   K132909

3. Comparison with predicate:

Table 1. Comparison with Predicate Device

Similarities		
Item	Device: BD Phoenix Automated Microbiology System - GN Meropenem-vaborbactam (K173523)	Predicate: BD Phoenix Automated Microbiology System - GN Tigecycline (K132909)
Intended Use	Determination of *in vitro* antimicrobial susceptibility testing of aerobic and facultative anaerobic Gram-negative and Gram-positive bacteria	Same
Source of	Bacterial colonies isolated from	Same

Similarities		
Item	Device: BD Phoenix Automated Microbiology System - GN Meropenem-vaborbactam (K173523)	Predicate: BD Phoenix Automated Microbiology System - GN Tigecycline (K132909)
Microorganisms for Testing	culture	
Technology	Automated growth-based detection	Same
Methodology	Determination of MIC using serial two-fold dilution format	Same
Read Method	Automated	Same
Inoculation Methods	Manual: PhoenixSpec nephelometer Automated: BD Phoenix AP instrument	Same
Result Reported	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (S,I,R)	Same
Incubation	<16 hours	Same

Differences		
Item	Device: BD Phoenix Automated Microbiology System - GN Meropenem-vaborbactam (K173523)	Predicate: BD Phoenix Automated Microbiology System - GN Tigecycline (K132909)
Antimicrobial agent	Meropenem/vaborbactam	Tigecycline
Reporting Range	*Enterobacteriaceae* (except *Providentia* spp. and *P. mirabilis*): 0.125/8 - 32/8 µg/mL *P. mirabilis*: 0.5/8 – 32/8 µg/mL *Providentia* spp.: 2/8 – 32/8 µg/mL	0.25 - 16 µg/mL

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

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

2. CLSI M100-S027: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh Informational Supplement

3. CLSI M7-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition

L. Test Principle:

The BD Phoenix Automated Microbiology System is a broth based microdilution method that utilizes a redox indicator (colorimetric oxidation-reduction) to enhance detection of

organism growth. The MIC is determined by comparing growth in wells containing serial two-fold dilutions of an antibiotic to the growth in "growth control wells" that contain no antibiotic.

M. Performance Characteristics:

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was performed at three clinical sites using 15 isolates of non-fastidious Gram negative organisms. The isolates were tested at each site in triplicate over three different days using both inoculation methods (i.e., manual, BD Phoenix AP) resulting in 405 data points (15 strains x 3 replicates x 3 sites x 3 days= 405). The isolates tested in the reproducibility study included *C. koseri* (1), *E. cloacae* (4), *E. coli* (1), *K. pneumoniae* (4), and *P. aeruginosa* (5). The mode MIC value was pre-determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. There was one "off-scale" MIC result when inocula were prepared manually and three "off-scale" results when inocula were prepared using the BD Phoenix AP. The best and worst case reproducibility was calculated as described in the AST Special Controls Guidance document. The reproducibility results were acceptable as shown in Table 2.

Table 2. Summary of Reproducibility Studies- BD Phoenix Meropenem/vaborbactam.

Inoculation Method	Best Case	Worst Case
Manual PhoenixSpec Nephelometer	95.3% (386/405)	95.1% (385/405)
Phoenix AP Instrument	95.6% (387/405)	95.1% (385/405)

b. Linearity/assay reportable range:

Not Applicable

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

Quality Control Testing:
The QC isolates recommended by both FDA and CLSI, *E.coli* ATCC 25922, *E. coli* ATCC 35218, *K. pneumoniae* ATCC 700603, *K. pneumoniae* ATCC BAA 1705, and *P. aeruginosa* ATCC 27853 were tested a sufficient number of times (i.e., at least 20/site) at each of three testing sites. They were tested using both manual and Phoenix AP inoculation methods and read by the BD Phoenix instrument. The results are summarized in Table 3. Greater than 95% of the results was obtained for each inoculation method and were acceptable.

Table 3. Quality Control Results – Meropenem/vaborbactam

Organism	Conc (µg/mL)*	Reference	Inoculum Preparartion	
			Manual (PhoenixSpec)	Phoenix AP Inoculation
E. coli ATCC 25922 Expected Range: 0.008/8-0.06/8 µg/mL	0.004			
	0.008			
	0.015			
	0.03			
	0.06			
	≤0.125**	130	134	85
	0.25			
	0.5		1	
E. coli ATCC 35218 Expected Range: 0.008/8-0.06/8 µg/mL	0.004			
	0.008			
	0.015			
	0.03			
	0.06			
	≤0.125**	131	133	81
	0.25			
	0.5			1
	1			
	2			
	4			
	8		1	
	16		1	
K. pneumoniae ATCC 700603 Expected Result: 0.015/8-0.06/8 µg/mL	0.008			
	0.015			
	0.03			
	0.06			
	≤0.125**	127	132	85
	0.25			
	0.5	1	1	
	1			
	2	1		
K. pneumoniae ATCC BAA-1705 Expected Result: 0.015/8-0.06/8 µg/mL	0.008			
	0.015			
	0.03			
	0.06			
	≤0.125**	126	131	85
	0.25	2		
	0.5		1	
	1		1	
P. aeruginosa ATCC 27853 Expected Result: 0.125/8-1/8 µg/mL	0.06			
	≤0.125**	1		
	0.25	95	125	76
	0.5	29	10	6
	1	4	1	
	2			

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

**The lowest dilution of the Phoenix Meropenem/vaborbactam MIC range is ≤0.125 µg/mL. Obtaining this value was considered an indicator that the quality control test results were acceptable.

The expected range for *P. aeruginosa* ATCC 27853 is 0.125/8 – 1/8 µg/mL and all results were acceptable. However, the Phoenix MIC reporting range is 0.125/8 to 32/8 µg/mL and does not provide results lower than 0.125/8 µg/mL to cover the expected range for *E. coli* ATCC 25922 (0.008/8-0.06/8), *E. coli* ATCC 35218 (0.008/8-0.06/8), *K. pneumoniae* ATCC 700603 (0.015/8-0.06/8), and *K. pneumoniae* ATCC BAA-1705 (0.015/8-0.06/8). A MIC value of ≤0.125/8 µg/mL indicated that the results for these four QC organisms were acceptable.

The footnote is included in *Table 1, Quality Control Organisms and Expected Results* of the BD Phoenix meropenem/vaborbactam package insert.

- "*The lowest dilution of the BD Phoenix Automated Microbiology System meropenem/vaborbactam MIC range is ≤0.125/8 µg/mL. Obtaining this value was considered as an indicator that the quality control test results were acceptable.*"

Inoculum Density Check:
The BD PhoenixSpec Nephelometer was used to prepare the inocula for testing of the clinical, challenge, reproducibility, and QC isolates. The same inoculum suspension was used for both the Phoenix System and the reference method testing. The BD Phoenix AP instrument was used to standardize the inocula for challenge, QC, and reproducibility isolates. Validation data for both the PhoenixSpec and the Phoenix AP instrument was provided and found to be acceptable.

Growth Failure Rate

The growth rate for both inoculation methods was 99.9%.

Purity Check:

Purity check plates were performed on all isolates from each inoculum preparation.

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 the BD Phoenix Automated Microbiology System - GN Meropenem-vaborbactam (0.125/8-32/8 µg/mL) panel were compared to results obtained with the CLSI frozen broth microdilution reference panel. Reference panels were prepared according to CLSI M07-A10 guidelines. The range of dilutions evaluated with the panels was the same as the BD Meropenem/vaborbactam panel.

The BD Phoenix Spec Nephelometer, the primary inoculation method, was used to obtain a 0.50 – 0.60 McFarland for all challenge, clinical, QC, and reproducibility isolates. The BD Phoenix AP instrument, the secondary inoculation method, was used to test challenge, QC, and reproducibility isolates. It is designed to standardize the ID broth inoculum equivalent to the BD Phoenix Spec Nephelometer, add the preset amount of AST indicator broth to the AST broth tube, and transfer the required aliquot of ID broth inoculum to AST broth tubes.

Clinical:

Clinical testing was conducted at three sites using 900 fresh and 114 stock *Enterobacteriaceae* organisms for a cumulative of 1014 isolates. These consisted of *C. freundii* (37 isolates), *C. koseri* (42), *Citrobacter* species (22), *E. aerogenes* (61), *E. cloacae* (81), *Enterobacter* species (5), *E. coli* (283), *K. oxytoca* (57), *K. pneumoniae* (171), *M. morganii* (40), *P. mirabilis* (87), *Providencia* species (28), *P. stuartii* (27), *S. marcescens* (66), and *Serratia* species (7). Of the clinical isolates, one isolate was resistant to meropenem/vaborbactam by the reference method.

Challenge:

Additional stock challenge isolates were tested at each study site. These isolates consisted of organisms with known resistance mechanisms (e.g., isolates obtained from FDA/CDC AR bank) to challenge the ability of AST system to correctly identify the susceptibility category. Challenge testing was conducted using 127 *Enterobacteriaceae* organisms including *C. freundii* (16 isolates), *C. koseri* (2), *E. aerogenes* (3), *E. cloacae* (27), *E. coli* (33), *K. oxytoca* (10), *K. pneumoniae* (31), *P. mirabilis* (3), and *S. marcescens* (2). Of these 127 challenge isolates, 9 were resistant to meropenem/vaborbactam by the reference method.

A total of 10 resistant strains of *Enterobacteriacea*e were evaluated. No resistant strains of the following species were evaluated: *C. freundii*, *C. koseri*, *E. aerogenes*, *E. coli*, *K. oxytoca*, *M. morganii*, *P. mirabilis*, *P. stuartii*, and *S. marcescens*. Only one isolate of *E. cloacae* was resistant. As a result, the sponsor included the following limitation in the device labeling:

> *The ability of the BD Phoenix AST system to detect resistance to meropenem/vaborbactam in the following species is unknown because resistant strains were not available or insufficient at the time of comparative testing: C. freundii*, *C. koseri*, *E. cloacae*, *E. aerogenes*, *E. coli*, *K. oxytoca*, *M. morganii*, *P. mirabilis*, *P. stuartii*, and *S. marcescens*.

Results for clinical and challenge isolates were evaluated separately and combined. Table 4 below illustrates the performance of testing meropenem/vaborbactam using the manual inoculation method only.

Table 4. Combined (Clinical and Challenge) Performance Summary of BD Phoenix with Clinical and Challenge *Enterobacteriaceae* Isolates – Manual Inoculation Method

Meropenem/ vaborbactam	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	Min	Maj	vmj
***Enterobacteriaceae* ≤4/8 (Susceptible), 8/8 (Intermediate), ≥16/8 (Resistant)**												
Clinical	1014	1004	99.0	15	7	46.7	1012	99.8	1	2	0	0
Challenge	127	124	97.6	11	8	72.7	127	99.2	9	1	0	0
Combined	1141	1128	98.9	26	15	57.7	1141	99.7	10	3	0	0

EA - Essential Agreement
CA - Category Agreement
R - resistant isolates
maj – major discrepancies
vmj - very major discrepancies
min – minor discrepancies

Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of BD Phoenix within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the BD Phoenix 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 BD Phoenix result.

The Phoenix meropenem/vaborbactam performance met the acceptance criteria for *Enterobacteriaceae* with overall EA an CA greater than 90%. However, given that the low combined evaluable EA% (57.7%) and the limited number of isolates with results around the breakpoints for analysis, the following limitation was included in the labeling to address the potential for misreporting the MIC particularly around the breakpoints:

Due to a small number of Enterobacteriaceae on-scale isolates available for comparative testing, there is limited data regarding performance of the BD Phoenix Gram-negative for meropenem/vaborbactam particularly around the breakpoints. Therefore, though rare, isolates with MIC values of 4/8, 8/8 and 16/8 µg/mL should be confirmed with an alternate method.

All *Enterobacteriaceae* isolates were tested using a panel with the dilution range of 0.125/8- 32/8 µg/mL *P. mirabilis* and *Providentia* species isolates were tested using this dilution range but showed low %EA and the sponsor submitted only truncated data and requested that the reportable range be truncated to 0.5/8 – 32/8 µg/mL for *P. mirabilis* and to 2/8 – 32/8 µg/mL for *Providencia* species. The EA and CA that were calculated were based on these truncated ranges and incorporated into the overall EA and CA. Results for organisms of these species will be reported based on this truncated range.

Trending

The performance of this device was evaluated for trending. There were only 55 results that were "evaluable" for trending compared to the reference MIC. The results show 25 MICs were below the reference (shift to the left), 8 were exact, and 22 were above (shift to the right). There was <30% (i.e., -5.45%) difference observed between lower versus greater and therefore, this is not considered indicative of a trend when comparing the device to the

reference method. No additional information was included in labeling regarding trending. See Table 5 for analysis. Data analyses was also conducted on each organism and similar results were observed.

Table 5: MIC Trending for all Combined (clinical and challenge) *Enterobacteriaceae* Isolates

Meropenem/ vaborbactam	Total	≥1 dil lower	Exact	≥1 dil higher
Enterobacteriaceae[a]	**55**	**25 (45.45%)**	**8 (14.55%)**	**22 (40.00%)**

[a]Difference between the higher and lower dilutions is -5.45%; 95% C.I. (-23.08% to 12.67%)

Reportable Ranges:

The Meropenem/vaborbactam performance evaluation was based on different reportable ranges for the organism groups as shown below:

≤0.125/8- ≥32/8 µg/mL for *Enterobacteriaceae* (except *P. mirabilis* and *Providentia* species)
≤0.5/8 - ≥32/8 µg/mL for *P. mirabilis*
≤2/8 - ≥32/8 µg/mL for *Providencia* species

Inoculum Preparation Methods:

The challenge organisms were also tested using suspensions prepared by the Phoenix AP instrument. The comparison between manual (PhoenixSpec) method and Phoenix AP is shown in Table 6. The overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. There were no very major or major discrepancies with either inoculation method.

Table 6: Comparison of Inoculation Methods with Challenge Isolates

Meropenem/ vaborbactam	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	Min	Maj	vmj
***Enterobacteriaceae* ≤4/8 (Susceptible), 8/8 (Intermediate), ≥16/8 (Resistant)**												
Manual (PhoenixSpec)	127	124	97.6	11	8	72.7	127	99.2	9	1	0	0
Phoenix AP	127	127	100	12	12	100	125	98.4	9	2	0	0

Enzyme Group Characterization/Resistance Markers Information:

Enterobacteriaceae with beta-lactamases were included in the meropenem/vaborbactam comparative studies. They were AmpC (6), KPC (16), OXA (9), CTX-M (8), TEM (14), and SHV (8). The *Enterobacteriaceae* included *C. freundii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, and *P. mirabilis*.

The study indicated that susceptibility to meropenem/vaborbactam can be variable with respect to beta lactamase type. For isolates where beta-lactamase type was known, eight

K. pneumoniae isolates demonstrated meropenem/vaborbactam resistance (>32/8 µg/mL) in the presence of AmpC, KPC, OXA, CTX-M, TEM, and/or SHV. However, twelve *K. pneumoniae* isolates showed susceptibility to meropenem/vaborbactam in the presence of KPC, OXA, CTX-M, TEM, and/or SHV.

The following limitation was added to the labeling regarding other resistance markers and enzyme characterization:

> *Enzyme group characterization was not available for some resistance mechanisms at the time of comparative testing, and therefore the performance of the BD Phoenix meropenem/vaborbactam is unknown for Enterobacteriaceae isolates in the presence SME, CMY, and ACT.*

b. Matrix comparison:

N/A

3. Clinical studies:

a. Clinical Sensitivity:

N/A

b. Clinical specificity:

N/A

c. Other clinical supportive data (when a. and b. are not applicable):

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Meropenem/vaborbactam are as listed in Table 7.

Table 7. 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 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.