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

A. 510(k) Number:

K132674

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Meropenem at concentrations of 0.125 – 32 µg/mL to Gram-negative ID/AST or AST only Phoenix panels to correspond to revised CLSI and FDA breakpoints for this drug.

C. Measurand:

Meropenem concentration of 0.125 - 32 µg/mL

D. Type of Test:

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

E. Applicant:

Becton, Dickinson and Company

F. Proprietary and Established Names:

BD Phoenix™ Automated Microbiology System – Meropenem 0.125 - 32 µg/mL

G. Regulatory Information:

1. Regulation section:

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

2. Classification:

   II

3. Product code:

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

   JWY – Manual Antimicrobial Susceptibility Test Systems

LRG – Instrument for Auto Reader and Interpretation of Overnight Susceptibility

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

83 Microbiology

H. Intended Use:

1. Intended use(s):

The BD Phoenix™ Automated Microbiology System is intended for *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*.

This premarket notification is for the addition of the antimicrobial agent meropenem at concentrations of 0.125 – 32 µg/mL to Gram-negative ID/AST or AST only Phoenix panels. Meropenem has been shown to be active *in vitro* against most strains of organisms listed below, as described in the FDA-approved package inserts for this antimicrobial agent.

Active *In Vitro* and in Clinical Infections Against:
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa

Active *In Vitro*
*Citrobacter koseri (*formerly *diversus)*
Citrobacter freundii
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii

Proteus vulgaris
Serratia marcescens

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   BD Phoenix Instrument and software

I. Device Description:

This submission is for a single drug in the gram negative ID/AST or AST only panel. The ID System was not reviewed.

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 5×10^5 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 $35^\circ C \pm 1^\circ C$.

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.

Meropenem is a penem antibacterial indicated as a single agent therapy for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, bacterial meningitis

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITEK System

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

   N50510

3. Comparison with predicate:

Table 1. Similarities and Differences of the BD Phoenix Meropenem and the Predicate

Similarities		
Item	Device	Predicate
	BD Phoenix Automated Microbiology System Meropenem 0.125–32 µg/mL	**VITEK (N50510)**
Intended Use	Determination of susceptibility to meropenem with members of *Enterobacteriaceae*	Same
Source of Organisms for testing	Bacterial colonies isolated from culture	Same
System	Automated instrumented system for *in vitro* antimicrobial susceptibility testing (AST) of bacteria from culture	Same
Incubation time	Short Incubation Test (<16 hours)	Same
Test Card	Containment card/panel to house the dried antimicrobials	Same

Similarities		
Item	Device	Predicate
	and substrates	
Results	MIC and categorical interpretations that include susceptible (S), intermediate (I), resistant (R) or not susceptible (N).	Same
Methodology	Tests antimicrobials in serial two-fold doubling dilution format to determine MIC results	Computer-assisted extrapolation of doubling dilutions to determine MIC results
Technology	Automated growth-based, enhanced by use of a redox indicator (colorimetric oxidation-reduction) to detect organism growth	Automated growth-based detection using attenuation of light measured by an optical scanner.

Differences		
Item	Device	Predicate
Methodology	Tests antimicrobials in serial two-fold doubling dilution format to determine MIC results	Computer-assisted extrapolation of doubling dilutions to determine MIC results
Technology	Automated growth-based, enhanced by use of a redox indicator (colorimetric oxidation-reduction) to detect organism growth	Automated growth-based detection using attenuation of light measured by an optical scanner.

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

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

CLSI M7-A8 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically

CLSI M100-S22 Performance Standards for Antimicrobial Susceptibility Testing

L. Test Principle:

The AST portion of 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 which contain no antibiotic.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility testing was conducted at two external sites and one internal site. Testing was performed using inocula prepared manually and standardized using both the PhoenixSpec nephelometer and using the BD Phoenix AP instrument. Results were compared to the modal range.

Twelve organisms with on-scale meropenem MIC values were provided to the testing sites by BD with isolate identification and expected MIC result blinded to the testers. Isolates were tested in triplicate on three separate days.

Results of inter-site and intra-site reproducibility studies were acceptable and demonstrated best-case and worst case of greater than 95%. A summary of the reproducibility study performance is illustrated in Table 2 below.

Table 2. Summary of Reproducibility Studies

BD Phoenix Instrument Platform	Inoculation Method	Best Case	Worst Case
BD Phoenix	AP Instrument	99.7%	99.4%
	Manual	98.1%	97.5%

Best case calculation for reproducibility assumes off-scale results are within one well from the mode MIC value. Worst case calculation for reproducibility assumes off-scale results are greater than one well from the mode MIC value.

b. Linearity/assay reportable range:

Not applicable

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

The FDA and CLSI recommended quality control isolates *E.coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were tested each day of the Challenge and Accuracy (Clinical) Studies with the reference method and with the BD Phoenix System. The inocula were standardized using both the automated (Phoenix AP) and manual (PhoenixSpec) inoculum dilution/standardization methods. A sufficient number of tests were performed and all quality control results for the BD Phoenix fell within the acceptable ranges demonstrating that the BD Phoenix System can consistently produce quality control results in the recommended range for meropenem.

Table 3. Summary of Quality Control Results

QC Organism	Expected MIC Range (µg/mL)	Concentration (µg/mL)	Inoculation Method			
			Manual		Phoenix AP	
			Reference QC	Phoenix QC	Reference QC	Phoenix QC
***E. coli* ATCC 25922**	**0.008 – 0.06**	≤0.125[†]	78	100	78	99
		0.25				
		0.5				
		1				
		2				
		4				
		8				
		16				
		32				
		>32				
***P. aeruginosa* ATCC 27853**	**0.25-1**	≤0.125				
		0.25	9	17	9	9
		0.5	59	84	59	87
		1	8		8	1
		2				
		4	1		1	
		8	1		1	
		16				
		32				
		>32				

[†]BD Phoenix Panel range for Meropenem is 0.125-32 ug/mL.

Growth Failure Rate: Seven isolates of Pseudomonas species failed to grow during the clinical study. The overall growth rate of 99.6% is acceptable.

Purity Check Plates: Purity check plates were inoculated from the standardized organism suspensions for both the Phoenix and reference methods. Any isolate that showed mixed growth on the purity check plate was considered noncompliant and not included in result analysis.

Inoculum Density Control: 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.

d. Detection limit:

Not applicable

e. Analytical specificity:

Not applicable

f. Assay cut-off:

No applicable

2. Comparison studies:

a. Method comparison with predicate device:

The accuracy of results obtained with the Phoenix System was determined by comparison to the CLSI-recommended broth dilution method (reference method). Reference panels were prepared according to CLSI M07-A8 guidelines. Sites performed testing on gram-negative isolates using Phoenix and reference panel formats appropriate for gram negative organisms. Antimicrobial agents in the test and reference panels had identical dilution ranges which were appropriate for the interpretive breakpoints of the drug. Testing was performed using at least two different production lots of Phoenix panels, AST broth and AST indicator at each study site. A minimum of three different lots of the Phoenix panel were used across all sites for the entire study. Phoenix and reference panels were inoculated using the same organism suspension.

Growth in the Phoenix panels was determined from data recorded by the instrument. Performance was analyzed using FDA breakpoints for meropenem, and results were compared to results obtained by the broth micro broth dilution reference method based on the guidelines provided in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems.*

A total of 1089 clinical isolates were tested at the three study sites and included both fresh and stock isolates. Stock isolates comprised 10.6% of total isolates tested. Clinical isolates tested included representatives of species listed in the FDA pharmaceutical drug label. Clinical isolates were tested using inocula prepared using the PhoenixSpec nephelometer (manual method).

A total of 113 challenge isolates were supplied to the testing sites by the sponsor. Challenge isolates were obtained from BD's internal collection and from external laboratories. Results obtained for Challenge isolates using the Phoenix System were compared to expected MIC results; expected MIC values and categorical interpretations were derived from testing with multiple lots of reference broth dilution panels over a three-month period. The challenge set was divided into subsets and an individual subset was distributed to each of the three study sites. Identification and

expected results were masked to the study sites. The inocula for the challenge isolates were prepared using both the PhoenixSpec nephelometer (manual method) and the Phoenix AP (automated method).

The performance evaluation summary of essential and categorical agreement results for clinical, and challenge isolates with inocula prepared using the PhoenixSpec nephelometer (manual method) is shown in the Table 4 below:

Table 4. BD Phoenix Meropenem (PhoenixSpec Nephelometer - Manual Inoculum Prep)

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#R	min	maj	vmj
Clinical												
Enterobacteriaceae	**906**	**899**	**99.2**	**33**	**30**	**90.9**	**899**	**99.2**	**37**	**5**	**1**	**1**
Pseudomonas combined species§	**183**	**165**	**90.2**	**145**	**133**	**91.7**	**172**	**94.0**	**23**	**9**	**2**	**0**
Total Clinical	**1089**	**1064**	**97.7**	**178**	**163**	**91.6**	**1071**	**98.3**	**60**	**14**	**3**	**1**
Challenge												
Enterobacteriaceae	**96**	**95**	**99.0**	**22**	**21**	**95.5**	**96**	**100**	**38**	**0**	**0**	**0**
Pseudomonas combined species	**17**	**17**	**100**	**15**	**15**	**100**	**17**	**100**	**9**	**0**	**0**	**0**
Total Challenge	**113**	**112**	**99.1**	**37**	**36**	**97.3**	**113**	**100**	**47**	**0**	**0**	**0**
Combined Clinical and Challenge	**1202**	**1176**	**97.8**	**215**	**199**	**92.6**	**1184**	**98.5**	**107**	**14**	**3**	**1**

§ The majority of clinical isolates were *P. aeruginosa*. Only 4 clinical isolates were *Pseudomonas* species.

Table 5. BD Phoenix Meropenem (Phoenix AP - Auto Inoculum Prep)

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#R	min	maj	vmj
Challenge												
Enterobacteriaceae	**97**	**96**	**99.0**	**24**	**23**	**95.8**	**96**	**99.0**	**39**	**1**	**0**	**0**
Pseudomonas combined species	**17**	**17**	**100**	**15**	**15**	**100**	**17**	**100**	**9**	**0**	**0**	**0**
Total Challenge	**114**	**113**	**99.1**	**39**	**38**	**97.4**	**113**	**99.1**	**48**	**1**	**0**	**0**

EA = Essential Agreement
CA = Category Agreement
R = Resistant 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 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.

For the clinical and challenge organism testing performed for meropenem using the BD Phoenix, the overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. There were 3 major errors (0.3%) (acceptance criteria ≤ 3%) and one very major error.

There were no instances of growth failure with either clinical or challenge isolates.

For challenge isolates two methods of organism suspension standardization were used in the evaluation of meropenem with the Phoenix System. Suspensions were prepared using both the PhoenixSpec nephelometer (manual method) and the Phoenix AP instrument (automated method). A comparison of the performance of the two standardization methods is illustrated in Table 6 below.

Table 6. Comparison of Challenge Isolate Inoculation Standardization Methods

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#R	min	maj	vmj
Inoculum Method												
PhoenixSpec (Manual)	**113**	**112**	**99.1**	**37**	**36**	**97.3**	**113**	**100**	**47**	**0**	**0**	**0**
Phoenix AP (Auto)	**114**	**113**	**99.1**	**39**	**38**	**97.4**	**113**	**99.1**	**48**	**1**	**0**	**0**

For the challenge organisms tested using suspensions prepared with either the manual (PhoenixSpec) method or using the Phoenix AP instrument, the overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. There was one minor error with inocula prepared using the Phoenix AP instrument and no very major errors with either inoculation method.

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:

   The MIC interpretive criteria are illustrated in Table 7 below.

Table 7. MIC Interpretive Criteria

Organism	**Meropenem - Susceptibility Interpretive Criteria (MIC in µg/mL)**		
	S	**I**	**R**
Enterobacteriaceae	≤ 1	2	≥ 4
Pseudomonas aeruginosa	≤ 4	8	≥ 16

N. Proposed Labeling:

The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information is complete and supports a substantial equivalence decision.