

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY**

**A. 510(k) Number:**

K123266

**B. Purpose for Submission:**

To obtain a substantial equivalence determination for the addition of ertapenem at concentrations of 0.0625-8.0 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:**

Ertapenem 0.0625 – 8.0 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 – Ertapenem 0.0625 – 8 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

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*.

**Ertapenem** 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:**

*Escherichia coli*  
*Klebsiella pneumoniae*  
*Proteus mirabilis*

**Active In Vitro**

*Citrobacter freundii*  
*Citrobacter koseri*  
*Enterobacter cloacae*  
*Klebsiella oxytoca* (excluding ESBL producing isolates)  
*Morganella morganii*  
*Proteus vulgaris*  
*Providencia rettgeri*  
*Providencia stuartii*  
*Serratia marcescens*

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

BD Phoenix Instrument and software

BD PhoenixSpec Nephelometer, BBL™ CrystalSpec™ nephelometer or 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 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  $5 \times 10^5$  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  $35^\circ \text{C} \pm 1^\circ \text{C}$ .

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.

Ertapenem is a penem antibacterial indicated for the treatment of moderate to severe infections caused by susceptible bacteria.

The MIC interpretive criteria for Ertapenem are as follows:

Organism	Susceptibility Interpretive Criteria (MIC in µg/mL)		
	S	I	R
<i>Enterobacteriaceae</i>	≤ 0.5	1	≥ 2

**J. Substantial Equivalence Information:**

1. Predicate device names(s)

VITEK System

2. Predicate 510(k) number(s)

N50510

3. Comparison with Predicate

Similarities		
Item	Device	Predicate
	<b>BD Phoenix Automated Microbiology System Ertapenem 0.0625-8 µg/mL</b>	<b>VITEK (N50510)</b>
<b>Intended Use</b>	Determination of susceptibility to ertapenem with members of <i>Enterobacteriaceae</i>	Same
<b>Source of Organisms for testing</b>	Bacterial colonies isolated from culture	Same
<b>System</b>	Automated instrumented system for in vitro antimicrobial susceptibility testing (AST) of bacteria from culture	Same
<b>Incubation time</b>	Short Incubation Test (<16 hours)	Same
<b>Test Card</b>	Containment card/panel to house the dried antimicrobials and substrates	Same
<b>Results</b>	MIC and categorical interpretations that include susceptible (S), intermediate (I), resistant (R) or not susceptible (N).	Same

<b>Differences</b>		
<b>Item</b>	<b>BD Phoenix Automated Microbiology System Ertapenem 0.0625-8 µg/mL</b>	<b>VITEK (N50510)</b>
<b>Methodology</b>	Tests antimicrobials in serial two-fold doubling dilution format to determine MIC results	Computer-assisted extrapolation of doubling dilutions to determine MIC results
<b>Technology</b>	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.

Ten on-scale organisms were provided to the testing sites by BD with isolate identification and expected MIC results blinded to the testers. Isolates were prepared

in triplicate on 3 non-consecutive days using each of the standardization methods.

Results of inter-site and intra-site reproducibility studies were acceptable and demonstrated best-case reproducibility of  $\geq 95\%$ .

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.

**Quality Control Results for Ertapenem with the Phoenix System:**

QC Organism	Expected MIC Range (µg/mL)	Concentration (µg/mL)	Inoculation Method	
			PhoenixSpec	Phoenix AP
<i>E. coli</i> ATCC 25922	0.004 – 0.015	≤ 0.0625	97	96
		0.125		
		0.25		
		0.5		
		1		
		2		
		4		
		8		
		> 8		
		Non-compliant		
<i>P. aeruginosa</i> ATCC 27853	2 - 8	≤ 0.0625		
		0.125		
		0.25		
		0.5		
		1		
		2	1	2
		4	96	85
		8	1	7
		> 8		
		Non-compliant		

A sufficient number of tests were performed and all quality control results fell within the acceptable ranges demonstrating that the BD Phoenix System can consistently produce quality control results in the recommended range for ertapenem.

**Growth Failure Rate:** All clinical isolates tested grew in the Phoenix panels; the overall growth rate was 100%.

**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 reference method testing. The BD Phoenix AP instrument and the BD PhoenixSpec were used to standardize the inocula for challenge, QC and reproducibility isolates. The calibration of both instruments was verified each day of testing. Validation data for both the PhoenixSpec and the Phoenix AP instrument was provided and found to be acceptable.

- d. *Detection limit:*  
No applicable
  - e. *Analytical specificity:*  
Not applicable
  - f. *Assay cut-off:*  
Not 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) at three testing sites in the U.S. 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 ertapenem, and results were compared to results obtained in the reference method based on the guidelines provided in the Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems.

A total of 1064 clinical isolates were tested at the three study sites and included both fresh and stock isolates. Clinical isolates tested included representatives of all species listed in the FDA pharmaceutical drug label. Clinical isolates were tested using inocula prepared using the PhoenixSpec nephelometer.

A total of 137 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 microbroth 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 (primary method) and the Phoenix AP instrument (secondary method).

In response to a request from the FDA, additional challenge isolates, some with MICs close to the established breakpoints, were tested in house. Results from these additional isolates are included in the Challenge isolate results below.

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

**Accuracy Summary, Clinical and Challenge Isolates**

	<b>Tot</b>	<b>EA N</b>	<b>EA %</b>	<b>Eval EA Tot</b>	<b>Eval EA N</b>	<b>Eval EA %</b>	<b>CA N</b>	<b>CA %</b>	<b>#R</b>	<b>min</b>	<b>maj</b>	<b>vmj</b>
<b>Clinical</b>	<b>1064</b>	<b>1052</b>	<b>98.9</b>	<b>68</b>	<b>60</b>	<b>88.2</b>	<b>1046</b>	<b>98.3</b>	<b>40</b>	<b>16</b>	<b>2</b>	<b>0</b>
<b>Challenge</b>	<b>137</b>	<b>133</b>	<b>97.1</b>	<b>36</b>	<b>32</b>	<b>88.9</b>	<b>130</b>	<b>94.9</b>	<b>70</b>	<b>7</b>	<b>0</b>	<b>0</b>
<b>Combined</b>	<b>1201</b>	<b>1185</b>	<b>98.7</b>	<b>104</b>	<b>92</b>	<b>88.5</b>	<b>1176</b>	<b>97.9</b>	<b>110</b>	<b>23</b>	<b>2</b>	<b>0</b>

**EA** = Essential Agreement  
**R** = Resistant Isolates  
**maj** = major discrepancies

**CA** = Category Agreement  
**min** = minor 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 ertapenem using the BD Phoenix, the overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. There were 2 major errors (0.2%) (acceptance criteria  $\leq$  3%) and no very major errors.

Essential agreement of evaluable results was 88.5%, partly due to a limited number of on-scale results for both clinical and challenge isolates. The majority of isolates that gave Phoenix results that differed from the reference method by more than one serial two-fold dilution showed more resistance than did the reference method. Overall there were 2 major errors and no very major errors.

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 ertapenem with the Phoenix System. Suspensions were prepared using both the PhoenixSpec (manual method) and the automated Phoenix AP instrument (automated method).

**Comparison of Challenge isolate inoculum standardization methods:**

Inoculation Method	Tot	EA N	EA %	Eval Tot	Eval EA	Eval EA %	CA N	CA %	#R	min	maj	vmj
Manual	137	133	97.1	36	32	88.9	130	94.9	70	7	0	0
Phoenix AP	138	132	95.6	36	30	83.3	130	94.2	71	7	1	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%. For both methods, all of the evaluable Phoenix results that differed from the reference method by more than one serial two-fold dilution showed more resistance than did the reference method. There was one major 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:

Organism	Ertapenem - Susceptibility Interpretive Criteria (MIC in µg/mL)		
	S	I	R
<i>Enterobacteriaceae</i>	≤ 0.5	1	≥ 2

**N. Proposed Labeling:**

The labeling is sufficient and satisfies the requirements for 21 CFR section 809.10.

**O. Conclusion:**

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