

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

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

K151320

**B. Purpose for Submission:**

This premarket notification 510(k) is for the removal of a limitation for testing *Enterobacter aerogenes* with Ertapenem 0.0625-4µg/mL on the BD Phoenix Automated Microbiology System gram-negative ID/AST or AST only Phoenix panels (original clearance K123266, June 26, 2013).

**C. Measurand:**

Ertapenem 0.0625 –8µg/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 – 8µg/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 aerogenes***  
*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:**

The BD Phoenix Automated Microbiology System (Phoenix System) is an automated system for the rapid identification (ID) and antimicrobial susceptibility testing (AST) of clinically relevant bacterial isolates. The system includes the following components:

- BD Phoenix instrument and software.
- BD Phoenix panels containing biochemical for organism ID testing and antimicrobial agents for AST determinations.
- BD Phoenix ID Broth used for performing ID tests and preparing AST Broth inoculum.
- BD Phoenix AST Broth used for performing AST tests only.
- BD Phoenix AST Indicator solution added to the AST Broth to aid in bacterial growth determination.

The Phoenix panel is a sealed and self-inoculating molded polystyrene tray with 136 micro-wells containing dried reagents. Organisms for susceptibility testing must be a pure culture and preliminary identified as a Gram-negative or Gram-positive isolate. Phoenix panels are inoculated with a specified organism density and placed into the instrument. Inoculum for use with the Phoenix system may be prepared either manually or may be automated using the BD Phoenix AP System.

The Phoenix AST method is a broth based microdilution test. The Phoenix System utilizes a redox indicator for the detection of organism growth in the presence of an antimicrobial agent. Measurements of changes to the indicator as well as bacterial turbidity are used in the determination of bacterial growth. Each AST panel configuration contains several antimicrobial agents with a wide range of two-fold doubling dilution concentrations.

The instrument houses the panels where they are continuously incubated at a nominal temperature of  $35^{\circ} \pm 1^{\circ}\text{C}$ . The instrument takes readings of the panels every 20 minutes. The readings are interpreted to give an identification of the isolate, minimum inhibitory concentration (MIC) values and category interpretations, S, I, R (susceptible, intermediate, or resistant). For some

organism/drug combinations with susceptible/non-susceptible interpretation, the category N (non-susceptible) is used.

**J. Substantial Equivalence Information:**

1. Predicate device names(s)

VITEK System

2. Predicate 510(k) number(s)

N50510

3. Comparison with Predicate

<b>Similarities</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
	<b>BD Phoenix Automated Microbiology System Ertapenem 0.0625-8 µg/mL</b>	<b>VITEK (N50510)</b>
<b>Intended Use</b>	The BD Phoenix Automated Microbiology System is intended for the rapid identification and in vitro antimicrobial susceptibility testing of isolates from pure culture of most aerobic and facultative anaerobic Gram-negative and Gram-positive bacteria of human origin.	Same
<b>Sample</b>	Isolated colonies from culture	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 Reported</b>	Minimum inhibitory concentration (MIC) and categorical interpretation (S/I/R)	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 (AST) Systems; Guidance for Industry and FDA – August 28, 2009.

CLSI M7-A8 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Eight Edition

CLSI M100-S22 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-second Informational Supplement

**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:*

In the original 510(k) pre-market submission cleared for the addition of ertapenem to the Gram negative ID/AST or AST only Phoenix panels (K123266), reproducibility testing was conducted at two external sites and one internal site. Results of inter-site and intra site reproducibility studies were acceptable and demonstrated best-case reproducibility of  $\geq 95\%$ .

In support of the current 510(k) submission, no new reproducibility studies

were conducted. However, the drug reporting range in the current 510(k) pre-market submission is 0.0625-4µg/ml for *Enterobacter aerogenes* compared to 0.0625-8µg/mL in original 510(k) K123266. This decrease in drug range resulted in fewer than 10 strains for reproducibility. Eight on-scale organisms were re-analyzed using the modified algorithm.

Re-analyzed results of inter-site and intra-site reproducibility studies were acceptable and demonstrated best-case reproducibility of ≥ 95% for both inocula prepared manually or with the BD Phoenix AP instrument.

*b. Linearity/assay reportable range:*

Not applicable

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

In the original 510(k) pre-market submission cleared for the addition of ertapenem to the Gram negative ID/AST or AST only Phoenix panels (K123266), the FDA and CLSI recommended quality control isolates *E.coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were tested each day of testing with the CLSI 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.

In this current 510(k) pre-market submission, daily QC testing was performed during the conduct of both the validation study of the revised algorithm and the additional internal study requested by the FDA. The results of QC testing are summarized in Table 1 below. The expected MIC range for ertapenem/*E.coli* ATCC 25922 is below the reporting range of the device and reference panels. Therefore, the MIC range for ertapenem/*P. aeruginosa* ATCC 27853 was used to assess the QC acceptance criteria.

**Table 1. MIC distribution for Quality Control Organisms Validation and Additional Internal Study Combined**

QC Organism	Expected MIC Range (µg/mL)	Concentration (µg/mL)	Inoculation Method		
			Reference Method	Manual PhoenixSpec	Automated Phoenix AP
<i>E. coli</i> ATCC 25922	0.004 – 0.015	≤ 0.0625	7	7	7
		0.125			
		0.25			
		0.5			
		1			
		2			

QC Organism	Expected MIC Range (µg/mL)	Concentration (µg/mL)	Inoculation Method		
		4			
		>4			
<i>P. aeruginosa</i> ATCC 27853	2 – 8	≤ 0.0625			
		0.125			
		0.25			
		0.5			
		1			
		2			
		4	7	7	6
		>4			1

QC results met the acceptance criteria and fell within the expected range 100% of the time in the reference and for the Phoenix System.

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:*

In the original 510(k) pre-market submission cleared for the addition of ertapenem to the Gram negative ID/AST or AST only Phoenix panels (K123266), *Enterobacter aerogenes* did not meet the expected performance and the following limitation was added to the labeling:

*Results for the following antimicrobial/organism combination(s) are suppressed from reporting by the BD Phoenix System:*

*Ertapenem: Enterobacter aerogenes*

This 510(k) pre-market submission was submitted in support of the removal of the limitation for *Enterobacter aerogenes* with Ertapenem on gram-negative ID/AST or AST only Phoenix panels, as indicated above. In addition, the reporting range for *E. aerogenes* was changed from 0.0625-8µg/mL to

0.0625-4µg/mL. The drug range for all other gram negative organism group remains unchanged from the original submission 0.0625-8µg/mL.

**Algorithm Modification:**

BD determined that the cause of the decreased performance for *Enterobacter aerogenes* and ertapenem in the original 510(k) pre-market submission (K123266) was due to the device algorithm which biased the ertapenem MIC value by one two-fold doubling dilution higher than that of the reference method. To adjust for this bias the device algorithm was modified to utilize the 8µg/mL well MIC result for the 4µg/mL well result. This algorithm change was specific only to *Enterobacter aerogenes* (see Table 2).

**Table 2. Performance of *E. aerogenes* With Ertapenem Range (0.0625-8µg/mL) (K123266) vs. Range (0.0625-4µg/mL) (Modified Algorithm)**

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
<b>K126233 Ertapenem (0.0625-8µg/mL)</b>												
<b>Challenge Manual Preparation</b>	3	3	100	1	1	100	3	100	3	0	0	0
<b>Clinical</b>	46	33	71.7	18	7	38.9	37	80.4	1	8	1	0
<b>Combined</b>	49	36	73.5	19	8	42.1	40	81.6	4	8	1	0
<b>Modified Algorithm Ertapenem utilizes the 8 µg/mL well for 4 µg/mL</b>												
<b>Challenge-Manual Preparation</b>	3	3	100	1	1	100	3	100	3	0	0	0
<b>Challenge AP Preparation</b>	3	3	100	1	1	100	3	100	3	0	0	0
<b>Clinical Manual</b>	46	43	93.5	17	14	82.4	45	97.8	1	1	0	0
<b>Combined</b>	49	46	93.9	18	15	83.3	48	98	4	1	0	0

**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.

The data re-analysis demonstrated that performance of *Enterobacter aerogenes* is improved using the modified algorithm.

### **Validation Study:**

To validate the algorithm modification, testing was performed at BD using 90 *Enterobacter aerogenes* strains read at MIC 4 and > 4 µg/mL. Comparative testing results using both the CLSI reference broth microdilution and the Phoenix system using the adjusted algorithm are summarized in Table 3.

**Table 3. Validation Study  
(Performance of *E. aerogenes* with the adjusted algorithm)**

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
<b>Manual</b>	90	90	100	36	36	100	86	95.6	16	4	0	0
<b>AP</b>	90	90	100	35	35	100	84	93.3	16	6	0	0

In the validation study (Table 3), testing of 90 *E. aerogenes* isolates for ertapenem using the modified algorithm demonstrated that the overall %EA and % CA met the acceptance criteria of greater than or equal to 90%. No very major or major errors were observed with either inoculation method.

### **Additional Internal Study:**

In response to a request from the FDA, BD conducted an additional internal study using the modified algorithm. The study included testing of a total of 129 (105 clinical and 24 challenge) *Enterobacter aerogenes* isolates. The 105 clinical isolates consisted of 54 fresh and 51 stock strains collected within the past three years. The accuracy of results obtained with the Phoenix System was determined by comparison to the CLSI reference broth microdilution method. CLSI Reference panels included the drug range of (0.0625- 8 µg/ml) and (0.0625- 4µg/mL) and compared to the Phoenix panel for *E. aerogenes* (0.0625-4 µg/mL). Testing was performed with isolate inocula prepared manually (primary method) and prepared with the BD Phoenix AP instrument as summarized in Tables 4 and 5 below.

**Table 4. Performance of Clinical and Challenge Isolates Additional Internal Study (Manual Preparation)**

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
<b>Clinical</b>	105	100	95.2	51	47	92.2	100	95.2	12	4	1	0
<b>Challenge</b>	24	24	100	14	14	100	24	100	6	0	0	0
<b>Combined</b>	129	124	96.1	65	61	93.9	124	96.1	18	4	1	0

**Table 5. Performance of Clinical and Challenge Isolates Additional Internal Study (Phoenix AP Preparation)**

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
<b>Clinical</b>	105	98	93.3	50	44	88.0	97	92.4	12	5	3	0
<b>Challenge</b>	24	22	91.7	14	12	85.7	22	91.7	6	2	0	0
<b>Combined</b>	129	120	93	64	56	87.5	119	92.2	18	7	3	0

In the additional internal study (summarized in Table 4 and 5 above), testing of clinical and challenge isolates of *E. aerogenes* for ertapenem using the BD Phoenix System, demonstrated that the overall % EA and % CA met the acceptance criteria of greater than or equal to 90%. There was one major error (0.9%) observed with the manual inoculum preparation method. There were three major errors (2.8%) observed with the AP inoculum preparation method (acceptance criteria  $\leq 3\%$ ). No very major errors were observed with either inoculation method.

**Validation and Additional Studies Combined:**

The internal study data, a total of 129 *E. aerogenes* isolates (105 clinical and 24 challenges), were added to the data from previously run validation study which consisted of 90 isolates for a total of 219 *E. aerogenes* isolates. Testing in both studies was performed using both the PhoenixSpec (manual method) and the automated Phoenix AP instrument (automated method). The data is summarized in Table 6.

**Table 6. Performance Summary Clinical and Challenge Isolates Validation and Additional Studies**

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
<b>Manual Method</b>	219	214	97.7	101	97	96	210	95.9	34	8	1	0
<b>AP Preparation</b>	219	210	95.9	99	91	91.9	203	92.7	34	13	3	0

The overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90% for the manual inoculum preparation method. There was one major error (0.6%) and no very major errors.

The overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90% for isolate inocula prepared with BD Phoenix AP instrument. There were three major errors (1.7%) and no very major errors.

The data for both validation and internal studies showed acceptable performance for ertapenem and *E. aerogenes*.

**Resistant Isolates:**

The data of the 219 *E. aerogenes* isolates provided by the sponsor in the diagonal table format, showed that only 12 on-scale resistant isolates (35.3%) at the MIC range of 2-4 µg/mL were tested. The majority 22 out of 34 (64.7%) of resistant isolates tested resulted in MICs of > 4µg/mL or were not within essential agreement. Similarly, in the AP inoculum preparation, only 10 on-scale resistant *E. aerogenes* isolates (29.4%) at MIC range 2-4 µg/mL were observed. The majority (24 out of 34 or 70.6%) resistant isolates tested were either not evaluable or not within the essential agreement. This was addressed by adding the following footnote to the labeling:

*“Due to an insufficient number of on-scale resistant Enterobacter aerogenes available during comparative testing, the performance of BD Phoenix Automated System for isolates with MIC range of 2-4 µg/mL is unknown.”*

**Growth Rate:**

The growth rate of the 219 isolates tested in the Phoenix System during both the validation and additional studies was 100% for both preparation systems (manual and BD Phoenix AP instrument). This meets the acceptance criteria of < 10% non-growth of organisms tested.

**MIC Trends:**

Using the data provided by the sponsor in the diagonal table format recommended in the AST Guidance, an analysis was conducted to check for trending in MIC values.

As shown in Table 7, the data for *E. aerogenes* demonstrated an upward trend of one doubling dilution in the MIC of ertapenem on the Phoenix Panel as compared to the reference method 26.9% of the time, for the manual inoculum preparation method and 28% of the time for the AP inoculum preparation method. This may raise concerns for potential major errors.

**Table 7. Trending of Results For *Enterobacter aerogenes***

	Difference in MIC as Compared to the CLSI Reference Method					
	-2	-1	0	+1	+2	+ ≥3
Manual Combined (validation, internal and re-analyzed data)	0% (1/268)	3.7% (10/268)	66.4% (178/268)	26.9% (72/268)	2.2% (6/268)	0% (1/268)
AP inoculum Preparation (validation and internal additional study)	0% (0/219)	3% (7/219)	64% (141/219)	28% (62/219)	4% (8/219)	0% (1/219)

This higher MIC trend was addressed by adding the following footnote in the labeling:

*“The BD Phoenix Ertapenem MIC values tended to be one doubling dilution higher when testing Enterobacter aerogenes (n=268) by the manual and the AP inoculation methods compared to broth micro-dilution”.*

- 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.