

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
**DECISION MEMORANDUM**  
**ASSAY ONLY TEMPLATE**

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

K142170

**B. Purpose for Submission:**

Addition of Tigecycline to the BD Phoenix Gram positive ID/AST and AST only panels.

**C. Measurand:**

Tigecycline 0.0313 - 4 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

**G. Regulatory Information:**

1. Regulation section:

21 CFR 866.1645 – Short-Term Antimicrobial Susceptibility Test System

2. Classification:

Class 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 *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*.

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 bacterial 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 tigecycline at concentrations of 0.0313-4µg/mL to Gram-positive ID/AST or AST only Phoenix panels. Tigecycline has been shown to be active *in vitro* against most strains of microorganisms listed below, as described in the FDA-approved package inserts for this antimicrobial agent.

**Active *In Vitro* and in Clinical Infections Against:**

*Enterococcus faecalis* (vancomycin-susceptible isolates)

*Staphylococcus aureus* (including methicillin-susceptible and –resistant isolates)

3. Special conditions for use statement(s):

For prescription use only.

The current absence of resistant isolates precludes defining any results other than “Susceptible”. Isolates yielding MIC result suggestive of “Non-susceptible” category should be submitted to a reference laboratory for further testing.

4. Special instrument requirements:

For use with the BD Phoenix™ Automated Microbiology System

**I. Device Description:**

The BD Phoenix™ Automated Microbiology System includes instrumentation and software, sealed and self-inoculating molded polystyrene trays with 136 micro-wells containing dried reagents, and specific inoculum broth formulations for identification (ID) and antimicrobial susceptibility testing (AST). The organism to be tested must be in pure culture and preliminarily identified as Gram-positive or Gram-negative. Colonies are then suspended in the ID broth, and, using one of the recommended BD nephelometer devices, brought to a concentration of 0.5 McFarland. A further dilution is made into the AST broth. Prior to inoculation of the panel, an AST broth indicator is added which changes the AST broth to a blue color. The AST broth is a cation-adjusted formulation of Mueller-Hinton broth containing 0.01% Tween 80, and has a final isolate concentration of approximately  $5 \times 10^5$  CFU/mL. After inoculation and incubation, the AST broth indicator in the AST broth changes from blue to pink to colorless as organism growth and reduction in the panel well occurs. Inoculated panels are barcode scanned and loaded into the BD Phoenix™ Automated Microbiology System instrument where the panels are incubated at 35°C and continuously monitored for changes in the indicator and bacterial turbidity to determine bacterial growth in the presence of an antimicrobial agent. Organisms killed or inhibited by a given antimicrobial do not cause reduction of the indicator and therefore do not produce a color change. Additional interpretation is done using the software driven “EXPERT” System triggered rules derived from the CLSI standards and/or FDA drug labeling. Readings are taken every 20 minutes and a final AST result in 4 to 16 hours. The AST result is determined via automated readings; no manual readings are possible with this system.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

Vitek® Antimicrobial Susceptibility Test System

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

N50510

3. Comparison with predicate:

**Table 1. Similarities and Differences of the BD Phoenix Tigecycline and the Predicate**

<b>Similarities</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
	<b>BD Phoenix Automated Microbiology System (Tigecycline)</b>	<b>VITEK (N50510)</b>
<b>Intended Use</b>	Determination of <i>in vitro</i> antimicrobial susceptibility testing of aerobic and facultative anaerobic Gram-negative and Gram-positive bacteria	Same
<b>Source of Microorganisms for Testing System</b>	Bacterial colonies isolated from culture	Same
<b>Incubation Time</b>	Automated instrumentation for <i>in vitro</i> antimicrobial susceptibility testing (AST)	Same
<b>Test Card</b>	Short-term (<16 hours)	Same
<b>Results</b>	Contains dried antimicrobials and substrates	Same
<b>Technology</b>	MIC and interpretive criteria (i.e., susceptible, intermediate, resistant and non-susceptible)	Same
	Automated growth-based detection	Same

<b>Differences</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
<b>Methodology</b>	MIC determination based on serial two-fold dilution format	MIC determination based on computer assisted extrapolation of doubling dilutions
<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):**

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

- CLSI M100-S22 “Performance Standards for Antimicrobial Susceptibility Testing”
- Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test Systems; Guidance for Industry and FDA

#### **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 (if/when applicable):**

##### 1. Analytical performance:

###### *a. Precision/Reproducibility:*

Two separate reproducibility studies were conducted for each inoculum preparation method. Reproducibility testing using inocula prepared manually (PhoenixSpec Nephelometer) was conducted at two external and one internal site. Fourteen isolates with on-scale MIC values as pre-determined by reference methods were provided to the testing sites by BD. Isolate identification and expected MIC result was blinded to those conducting the testing. Testing was performed in triplicate on three separate days.

Reproducibility testing using inocula prepared by the automated (Phoenix AP) instrument was conducted at two external sites and one internal site. Testing was conducted using 14 isolates with on-scale MIC values. Isolate identification and expected MIC result was blinded to those conducting the testing. Testing was performed in triplicate on three separate days.

Results of the inter-site and intra-site reproducibility studies were acceptable and demonstrated best case and worst case results 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 Tigecycline - Gram Positive

<b>BD Phoenix Instrument Platform</b>	<b>Inoculation Method</b>	<b>Best Case</b>	<b>Worst Case</b>
BD Phoenix	Phoenix AP Instrument	100%	100%
	Manual PhoenixSpec Nephelometer	100%	100%

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

Regarding both the manual inoculation method, and the automated inoculation method (AP Instrument), no MIC results were off-scale. There were a total of 378 MIC values evaluated for the manual inoculation method and likewise a total of 378 MIC values evaluated for the automated inoculation method (AP Instrument).

*b. Linearity/assay reportable range:*

Not applicable

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

Testing of the FDA and CLSI recommended quality control (QC) strains, *S. aureus* and *E. faecalis* was performed each day of the challenge and clinical study testing with the reference method and with the BD Phoenix System. The inocula were standardized using both the automated (Phoenix AP) and manual (PhoenixSpec Nephelometer) methods. A sufficient number of tests were performed and all quality control results for the BD Phoenix fell within the acceptable ranges as per the FDA drug label, demonstrating that the BD Phoenix System can consistently produce quality control results in the recommended range for tigecycline.

Quality control testing of the BD Phoenix Tigecycline was conducted using two recommended QC strains. A total of 275 results were obtained for *S. aureus* ATCC 29213 and 275 for *E. faecalis* ATCC 29212. Results demonstrate that acceptable results were achieved >95% of the time by both auto-dilution and manual dilution inoculum preparation methods as shown in Table 3 and Table 4 below.

Table 3. Quality Control Results – BD Phoenix Tigecycline  
*S. aureus* ATCC 29213

ORGANISM	Tigecycline (µg/mL)	Reference	Auto-Dilution (Phoenix AP)	Manual Dilution (Phoenix Spec™)
<i>S. aureus 29213</i> Expected Range: 0.03 – 0.25 µg/mL	≤ 0.0313			
	0.0625	2	4	15
	0.125	66	78	99
	0.25	7	1	3
	Total	75	83	117

Table 4. Quality Control Results – BD Phoenix Tigecycline  
*E. faecalis* ATCC 29212

ORGANISM	Tigecycline (µg/mL)	Reference	Auto-Dilution (Phoenix AP)	Manual Dilution (Phoenix Spec™)
<i>E. faecalis 29212</i> Expected Range: 0.03 – 0.12 µg/mL	≤0.03		1	
	0.0625	45	76	99
	0.125	28	7	18
	0.25	1		
	Total	74	84	117

Growth Rate: The overall growth rate during the clinical studies was 99.7% (1150/1153).

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 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:*

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). Reference panels were prepared according to CLSI M07-A8 guidelines. In addition, specific to the drug tigecycline, fresh Mueller Hinton broth (<12 hours old) was used in the preparation of the reference panels. Sites performed testing on Gram positive isolates of *E. faecalis* and *S. aureus* using Phoenix and reference panel formats appropriate for these 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 tigecycline, and results were compared to results obtained by the broth microdilution reference method based on the guidelines provided in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems*.

A total of 977 clinical isolates were tested at the three study sites and included both fresh and stock isolates (783 *S. aureus*, 194 *E. faecalis*). 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 44 challenge isolates were supplied to the testing sites by the sponsor (30 *S. aureus*, 14 *E. faecalis*). 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 Table 4 below. The performance evaluation summary of essential and categorical agreement results for challenge isolates with inocula prepared using the Phoenix AP (automated method) is shown in Table 5 below.

**Table 4. BD Phoenix Tigecycline (PhoenixSpec Nephelometer - Manual Inoculum Preparation)**

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#NS	min	maj	vmj
<b>Clinical</b>												
<i>S. aureus</i> (methicillin-resistant and methicillin-susceptible isolates combined)	783	769	98.2	778	764	98.2	783	100	2	0	0	0
<i>E. faecalis</i> (vancomycin-susceptible isolates only)	193	187	96.9	182	182	100	193	100	0	0	0	0
<b>Challenge</b>												
<i>S. aureus</i> (methicillin-resistant and methicillin-susceptible isolates combined)	30	30	100	30	30	100	30	100	0	0	0	0
<i>E. faecalis</i> (vancomycin-susceptible isolates only)	14	14	100	14	14	100	14	100	0	0	0	0
<b>Combined Clinical and Challenge *</b>	1021	1001	98.0	1005	991	98.6	1021	100	2	0	0	0

\*Combined results include one isolate of *E. faecalis* with unknown vancomycin characterization.

**Table 5. BD Phoenix Tigecycline (Phoenix AP - Auto Inoculum Preparation)**

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#NS	min	maj	vmj
<b>Challenge</b>												
<i>S. aureus</i> (methicillin resistant and methicillin susceptible isolates combined)	30	30	100	30	30	100	30	100	0	0	0	0
<i>E. faecalis</i> (vancomycin susceptible isolates only)	14	14	100	14	14	100	14	100	0	0	0	0
<b>Combined Challenge</b>	44	44	100	44	44	100	44	100	0	0	0	0

**EA** = Essential Agreement  
**NS** = Non-susceptible  
**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 tigecycline using the BD Phoenix, the overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. Overall, there were no major, very major, or minor categorical errors.

The clinical data on *Staphylococcus aureus* demonstrated downward trending in the MIC of the BD Phoenix Tigecycline compared to the reference method. The following footnote to inform end users of the observed downward trending was added to the table in the package insert:

“BD Phoenix MIC values for isolates of *Staphylococcus aureus* may be lower by one dilution compared to reference broth microdilution”.

For challenge isolates two methods of organism suspension standardization were used in the evaluation of tigecycline 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	#NS	min	maj	vmj
<b>Inoculum Method</b>												
PhoenixSpec (Manual)	44	44	100	44	44	100	44	100	0	0	0	0
Phoenix AP (Auto)	44	44	100	44	44	100	44	100	0	0	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 were and no very major, major or minor categorical 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 - Tigecycline**

<b>Antibiotic Concentration Reviewed</b>	<b>Tigecycline - Susceptibility Interpretive Criteria (MIC in µg/mL)</b>		
Tigecycline 0.0313-4 µg/mL	<b>FDA (SIR)</b>	<b>BD Phoenix</b>	<b>CLSI</b>
<b>Organism</b>			
<i>Enterococcus faecalis</i> (vancomycin susceptible isolates)	≤ 0.25*, -, -	≤ 0.25*, -, -	Not Applicable
<i>Staphylococcus aureus</i> (including methicillin resistant isolates)	≤ 0.5*, -, -	≤ 0.5*, -, -	Not Applicable
<b>Quality Control Organisms</b>	<b>Expected Range</b>		
<i>Staphylococcus aureus</i> ATCC 29213	0.03-0.25	≤ 0.0313-0.25	0.03-0.25
<i>Enterococcus faecalis</i> ATCC 29212	0.03-0.12	≤ 0.0313-0.125	0.03-0.12

\*The current absence of resistant isolates precludes defining any results other than “Susceptible”. Isolates yielding MIC result suggestive of “Non-susceptible” category should be submitted to a reference laboratory for further testing.

**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.