Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K190905

B Applicant

Becton, Dickinson and Company

C Proprietary and Established Names

BD Phoenix Automated Microbiology System - GN Ceftaroline (0.0156-4 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645 - Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

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

B Measurand:

Ceftaroline 0.0156 - 4 µg/mL

C Type of Test:

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

III Intended Use/Indications for Use:

A 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*.

B 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*.

Ceftaroline 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:
Skin Infections and Community-Acquired Bacterial Pneumonia (CABP):
Gram-negative bacteria
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca

Active In Vitro but clinical significance is unknown:
Gram-negative bacteria
Citrobacter koseri
Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Proteus mirabilis

C Special Conditions for Use Statement(s):

- Rx - For Prescription Use Only
- Results for the following antimicrobic/organism combination(s) are suppressed from reporting by the BD Phoenix System:

Ceftaroline: *Morganella morganii*

- Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.

D Special Instrument Requirements:

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

IV Device/System Characteristics:

A 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°C ± 1°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 and/or the FDA-approved Ceftaroline drug label.

B Principle of Operation:

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.

C Instrument Description Information:

Modes of Operation	Yes	No
Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?	☒	☐
Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?	☐	☒
Software		
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types.	☒	☐

V Substantial Equivalence Information:

A Predicate Device Name(s):

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

B Predicate 510(k) Number(s):

K132909

C Comparison with Predicate(s):

Table 1: Comparison with the Predicate

Device & Predicate Device(s):	K190905	K132909
Device Trade Name	BD Phoenix Automated Microbiology System – GN Ceftaroline (0.0156-4 µg/mL)	BD Phoenix Automated Microbiology System – GN Tigecycline (0.25-16 µg/mL)
General Device Characteristic Similarities		
Intended Use/Indications For Use	Determination of in vitro antimicrobial susceptibility testing of aerobic and facultative anaerobic Gram-negative and Gram-positive bacteria	Same
Source of Microorganisms for Testing	Bacterial colonies isolated from culture	Same
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
General Device Characteristic Differences		
Antimicrobial Agent	Ceftaroline	Tigecycline
Indicated Organisms	Active In Vitro and in Clinical Infections Against: Gram-negative bacteria *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella oxytoca*	Active In Vitro and in Clinical Infections Against: Gram-negative bacteria *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella oxytoca* *Citrobacter freundii*

	Active In Vitro but clinical significance is unknown: Gram-negative bacteria *Citrobacter koseri* *Citrobacter freundii* *Enterobacter cloacae* *Enterobacter aerogenes* *Proteus mirabilis*	Active In Vitro but clinical significance is unknown: Gram-negative bacteria *Citrobacter koseri* *Enterobacter aerogenes* *Serratia marcescens*
Reporting Range	0.0156 – 4 µg/mL	0.25 – 16 µg/mL

VI Standards/Guidance Documents Referenced:

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

2. CLSI Supplement M100S: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh edition

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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study was performed at three clinical sites using 11 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 297 data points (11 strains x 3 replicates x 3 sites x 3 days = 297). The isolates tested in the reproducibility study included *C. freundii* (2), *E. cloacae* (2), *E. coli* (5), and *K. pneumoniae* ssp. *pneumoniae* (2). The reproducibility was calculated based on MIC values falling within ±1 dilution of the predetermined mode of the reference MIC values. There was one "off-scale" MIC result with manually prepared inocula and two "off-scale" results with inocula 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 Ceftaroline

Inoculation Method	Best Case	Worst Case
Manual PhoenixSpec Nephelometer	96.3% (286/297)	96.3% (286/297)
Phoenix AP Instrument	97.0% (288/297)	97.0% (288/297)

2. Linearity:

Not Applicable

3. Analytical Specificity/Interference:

Not Applicable

4. Assay Reportable Range:

Not Applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Quality Control Testing:

The CLSI recommended QC organism (*E.coli* ATCC 25922) was tested a sufficient number of times (i.e., at least 20/site) at each of three testing sites. It was tested using both manual and Phoenix AP inoculation methods and read by the BD Phoenix instrument. The results are summarized in Table 3. Results were acceptable for greater than 95% of tests performed using both inoculation methods.

Table 3. Quality Control Results – Ceftaroline

Organism	Conc (µg/mL)	Reference	BD Phoenix	
			Manual Inoculation (PhoenixSpec)	Phoenix AP Inoculation
E. coli ATCC 25922 Expected Range: 0.0313 -0.125 µg/mL	≤0.0156			
	0.03			
	0.06	75	56	42
	0.12	55	78	40
	0.25		1	2
	0.5			
	1			1
	2			
	4			
	>4			

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.

6. Detection Limit:

   Not Applicable

7. Assay Cut-Off:

   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Results obtained with the BD Phoenix Automated Microbiology System - GN Ceftaroline (0.015 - 4 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 reference panels was the same as that used for the BD Ceftaroline 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 832 fresh (91.8%) and 74 stock (8.2%) *Enterobacteriaceae* organisms for a total of 906 clinical isolates. These consisted of *C. freundii* (35 isolates), *C. koseri* (45), *Citrobacter* species (21), *E. aerogenes* (65), *E. cloacae* (81), *Enterobacter* species (5), *E. coli* (294), *K. oxytoca* (58), *K. pneumoniae* (180), *M. morganii* (36), and *P. mirabilis* (86). Of the clinical isolates, 174 isolates were determined to be resistant to ceftaroline 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 117 *Enterobacteriaceae* organisms including *C. freundii* (13), *C. koseri* (1), *E. aerogenes* (1), *E. cloacae* (28), *E. coli* (25), *K. oxytoca* (10), *K. pneumoniae* (36), and *P. mirabilis* (3). Of these 117 challenge isolates, 83 were resistant to ceftaroline by the reference method.

Results for clinical and challenge isolates were evaluated separately and combined. Table 4 below illustrates the performance of testing ceftaroline using the manual inoculation method only. To address testing of non-indicated species, the sponsor included the following statement in the Precautions section of the device labeling:

Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.

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

Ceftaroline	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	Min	Maj	vmj
***Enterobacteriaceae* ≤0.5 (Susceptible), 1 (Intermediate), ≥2 (Resistant)**												
Clinical	906	835	92.2	734	673	91.7	857	94.6	174	34	11	4
Challenge	117	116	99.1	36	35	97.2	117	100	83	0	0	0
Combined	1023	951	93	770	708	91.9	974	95.2	257	34	11	4

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 ceftaroline performance met the acceptance criteria for *Enterobacteriaceae* with overall EA an CA greater than 90%. However, when species were evaluated separately, *M. morganii* demonstrated an overall EA and CA of 47.2% and 69.4%, respectively. In addition, the major error rate and very major error rate for *M. morganii* was unacceptable at 26.9% (7/26) and 10% (1/10). Performance when testing this organism is therefore not acceptable. To address this, the following was included in the labeling:

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

- *Ceftaroline: Morganella morganii*

When performance was evaluated excluding *M. morganii* (Table 5), the overall EA and CA increased from 93.0% to 94.6% and 95.2% to 96.1%, respectively. In addition, the overall major error rate and very major rate was 0.6% (4/709) and 1.2% (3/249), respectively, and was deemed acceptable.

Table 5. Combined (Clinical and Challenge) Performance Summary of BD Phoenix with Clinical and Challenge *Enterobacteriaceae* Isolates Excluding *M. morganii* – Manual Inoculation Method

Ceftaroline	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	Min	Maj	vmj
***Enterobacteriaceae* ≤0.5 (Susceptible), 1 (Intermediate), ≥2 (Resistant)**												
Clinical	870	818	94	701	659	94	832	95.6	166	31	4	3
Challenge	117	116	99.1	36	35	97.2	117	100	83	0	0	0
Combined	987	934	94.6	737	694	94.2	949	96.1	249	31	4	3

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

Ceftaroline	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	Min	Maj	vmj
***Enterobacteriaceae* ≤0.5 (Susceptible), 1 (Intermediate), ≥2 (Resistant)**												
Manual (PhoenixSpec)	117	116	99.1	36	35	97.2	117	100	83	0	0	0
Phoenix AP	117	117	100	37	37	100	117	100	83	0	0	0

Enzyme Group Characterization/Resistance Markers Information:

Enterobacteriaceae with beta-lactamases were included in the ceftaroline comparative studies which consisted of the challenge isolates that were tested. Isolates with the following beta lactamases were included: AmpC (4), KPC (26), OXA (11), CTX-M (8), TEM (14), and SHV (9). The *Enterobacteriaceae* included *C. freundii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, and *P. mirabilis.*

Trending:

An analysis of trending was conducted using the combined clinical and challenge data for each organism group. This trending calculation considers MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method regardless of whether the device MIC values are on-scale. Results that are not clearly at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Trending analysis results are shown in Table 7; results were stratified by species to assess species-related trends. Species for which the difference between the percentage of isolates with higher or lower readings was ≥30 with a statistically significant confidence interval were considered to show evidence of trending. When combined *Enterobacteriaceae* isolates were assessed, there was no trending observed; however, when each species was evaluated separately, it was noted that MIC values for *C. koseri* and *P. mirabilis* trended higher when

compared to the reference method. Therefore, the following was included in the labeling to indicate this:

MIC values tended to be in exact agreement or at least one doubling dilution higher compared to the reference broth micro-dilution when testing the following:

- *Ceftaroline and C. koseri or P. mirabilis*

Table 7. MIC Trending Analysis of All Organisms (Clinical and Challenge)

Organism	Total Evaluable For Trending	≥1 Dilution Lower No. (%)	Exact No. (%)	≥1 Dilution Higher No. (%)	Percent Difference* (95% CI)	Trending Noted
C. freundii	30	3 (10)	17 (56.7)	10 (33.3)	23.3 (2.3 to 42.4)	No
C. koseri	44	1 (2.3)	23 (52.3)	20 (45.5)	43.2 (26.5 to 57.8)	Yes
Citrobacter spp.	13	2 (15.4)	7 (53.9)	4 (30.8)	15.4 (-17.0 to 44.4)	No
E. aerogenes	56	9 (16.1)	31 (55.4)	16 (28.6)	12.5 (-3.0 to 27.4)	No
E. cloacae	67	22 (32.8)	30 (44.8)	15 (22.4)	-10.5 (-25.0 to 4.7)	No
Enterobacter spp.	5**	0 (0)	1 (20)	4 (80)	80 (19.3 to 96.4)	No
E. coli	252	76 (30.2)	138 (54.8)	38 (15.1)	-15.1 (-22.2 to -7.8)	No
K. oxytoca	56	10 (17.9)	34 (60.7)	12 (21.4)	3.6 (-11.3 to 18.2)	No
K. pneumoniae	159	30 (18.9)	82 (51.6)	47 (39.6)	10.7 (1.3 to 19.9)	No
P. mirabilis	82	9 (11.0)	39 (47.6)	34 (41.5)	30.5 (17.3 to 42.4)	Yes
All *Enterobacteriaceae* (without *M. morganii)*	764	163 (21.3)	401 (52.5)	200 (26.2)	4.8 (0.6 to 9.1)	No

***** A positive percent difference indicates a higher MIC value compared to the reference method. A negative percent difference indicates a lower MIC value compared to the reference method.

****** Trending could not be evaluated due to low number of isolates.

2. Matrix Comparison:

Not Applicable

C Clinical Studies:

1. Clinical Sensitivity:

   Not Applicable

2. Clinical Specificity:

   Not Applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

D Clinical Cut-Off:

Not Applicable

E Expected Values/Reference Range:

The FDA-recognized susceptibility interpretive criteria for ceftaroline are as listed in Table 8.

Table 8. FDA-Recognized Interpretive Criteria* for Ceftaroline (µg/mL)

	Susceptible (S)	Intermediate (I)	Resistant (R)
Enterobacteriaceae	≤0.5	1	≥2

*FDA STIC Webpage
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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