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

A. 510(k) Number:

K172944

B. Purpose for Submission:

To obtain a substantial equivalence determination for Ceftazidime/Avibactam for testing of gram negative bacilli on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

C. Measurand:

The VITEK 2 AST-Gram Negative card contains the following concentrations of Ceftazidime/Avibactam: 0.06/4, 0.25/4, 1/4, 4/4, and 8/4 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The Ceftazidime/Avibactam MIC reporting ranges for the card are ≤ 0.12/4 – ≥16/4 µg/mL for *Enterobacteriaceae* and ≤ 0.25/4 – ≥16/4 µg/mL for *Pseudomonas aeruginosa*.

D. Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test for Ceftazidime/Avibactam

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK 2 AST- GN Ceftazidime/Avibactam (≤ 0.12 – ≥16 µg/mL)

G. Regulatory Information:

1. Regulation section:

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

2. Classification:

   Class II

3. Product code(s):

   LON – Fully automated short-term incubation cycle antimicrobial susceptibility system
   LTW – Susceptibility Test Cards, Antimicrobial
   LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   Microbiology, 83

H. Intended Use/Indications for Use:

1. Intended Use (s):

   The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.

2. Indications for Use:

   VITEK 2 AST-Gram Negative Ceftazidime/Avibactam is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of *in vitro* susceptibility to antimicrobial agents. VITEK 2 AST-Gram Negative Ceftazidime/Avibactam is a quantitative test. Ceftazidime/Avibactam has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

   Active both *in vitro* and in clinical infections
   Citrobacter species
   Enterobacter species
   Escherichia coli
   Klebsiella oxytoca
   Klebsiella pneumoniae
   Proteus mirabilis
   Pseudomonas aeruginosa

   The following *in vitro* data are available, but clinical significance is unknown:
   Citrobacter koseri
   Enterobacter aerogenes

Morganella morganii
Providencia stuartii
Serratia marcescens

The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.

3. Special conditions for use statement(s):

   For Prescription Use Only

   Limitations:

   - *Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):*
     - *Ceftazidime/Avibactam: Providencia rettgeri*
   - *Although within Essential Agreement when compared to the reference method, errors (major and/or very major) were observed due to the lack of intermediate category. Testing should be repeated using an alternative testing/reference method prior to reporting results for the following antibiotic/organism(s):*
     - *Ceftazidime/Avibactam: Pseudomonas aeruginosa when the VITEK 2 MIC is ≥16µg/mL due to observed major errors (4.1%), with an adjusted categorical major error rate of 1.2%.*

4. Special instrument requirements:

   VITEK 2 and VITEK 2 Compact Systems using VITEK 2 Systems 9.01 software

I. Device Description:

The VITEK 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK 2 AST card contains 64 wells. A control well(s) which contain only nutrient medium is resident on all cards. The remaining wells contain premeasured portions of antimicrobials combined with the nutrient media. The isolate to be tested is diluted to a standardized concentration with 0.45% to 0.50% saline before being used to rehydrate the antimicrobial medium within the card. The VITEK 2 System will automatically dilute the bacterial suspension to prepare an inoculum for susceptibility cards. Then the VITEK 2 will fill, seal and place the card into the incubator/reader. The VITEK 2 Compact has a manual filling, sealing and loading operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time (up to 24 hours for *Streptococcus* species). The analysis program determines when a well demonstrates growth based on attenuation of light measured by an optical scanner. This data is used to determine the minimum inhibitory concentration

or “MIC” values for the anti-microbial agent. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antimicrobial contained on the card.

VITEK 2 AST-GN Ceftazidime/Avibactam has the following concentrations in the card: 0.06/4, 0.25/4, 1/4, 4/4, and 8/4µg/mL (equivalent standard method concentration by efficacy in µg/mL). The Ceftazidime/Avibactam MIC result ranges for the VITEK 2 are:

- ≤ 0.12 – ≥ 16 µg/mL for *Enterobacteriaceae*
- ≤ 0.25 - ≥ 16 µg/mL for *Pseudomonas aeruginosa*

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITEK 2 AST-GN Ceftolozane/Tazobactam

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

   K161510

3. Comparison with predicate:

Table 1: Comparison with Predicate Device

Similarities		
Item	**Device: VITEK 2 AST-GN Ceftazidime/Avibactam (K172944)**	**Predicate Device: VITEK 2 AST-GN Ceftolozane/Tazobactam (K161510)**
Intended Use	The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.	Same
Test Method	Automated quantitative antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems to determine the *in vitro* susceptibility of Gram negative bacilli	Same
Inoculum	Standardized saline suspension of test organism	Same
Test Card	VITEK 2 Gram Negative Susceptibility Test Card	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Analysis Algorithm	Growth pattern analysis	Same
Differences		
Antimicrobial Agent	Ceftazidime/Avibactam	Ceftolozane/Tazobactam
Antimicrobial Concentrations	0.06/4, 0.25/4, 1/4, 4/4, and 8/4 µg/mL	0.5/4, 1/4, 4/4, 8/4, and 32/4 µg/mL
Reporting Range	*Enterobacteriaceae*: ≤0.12 - ≥16 µg/mL *P. aeruginosa*: ≤0.25 – ≥16 µg/mL	*Enterobacteriaceae* and *P. aeruginosa*: ≤ 0.25 - ≥32µg/mL

K. Standard/Guidance Documents Referenced (if applicable)

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

- CLSI M07-A10, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Ninth Edition" Vol. 35 No. 2 (January 2015)

- CLSI M100-S27, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-Fourth Informational Supplement, Vol. 37 No. 1 (January 2017)

L. Test Principle:

The VITEK 2 and VITEK 2 Compact Systems utilize automated growth-based detection using attenuation of light measured by an optical scanner. The optics in the systems uses visible light to directly measure organism growth within each of the 64 micro-wells. Transmittance optics is based on an initial light reading of a well before significant growth has begun. Every 15 minutes throughout the incubation cycle (defined period of time based on the VITEK 2 card), light transmittance readings of each well measures organism growth by the amount of light that is prevented from passing through the well. At the completion of the incubation period, the MIC values and their associated interpretive category results for each antimicrobial on the test card are displayed in an automatically generated report.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study for the VITEK 2 AST-GN card with Ceftazidime/Avibactam was conducted at three external clinical sites using ten isolates of gram-negative bacilli consistent with the Intended Use. Testing was performed on three separate days and in triplicate for a total of 270 data points. The isolates tested in the reproducibility study included one isolate each for *Klebsiella pneumoniae pneumoniae* and *Escherichia coli*, two isolates each for *Citrobacter freundii* complex, *Enterobacter aerogenes, Pseudomonas aeruginosa,* and *Serratia marcescens*. Inocula were prepared using both the auto-dilution and manual dilution methods for testing in the VITEK 2 System. Inocula were prepared by the manual dilution method only for use with the VITEK 2 Compact. The mode MIC value was determined and the reproducibility was calculated based on MIC values that fell within +/- one doubling dilution from the mode MIC value. The majority of data points were on-scale and within ± one doubling dilution agreement as compared to the mode MIC (Table 2). Two data points were off-scale when tested by the VITEK 2 and the VITEK 2 Compact. The data was analyzed taking into consideration best case and worst case scenarios as described in the Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems.

The reproducibility performance is shown in Table 2.

Table 2: Reproducibility Performance

	VITEK 2		VITEK 2 Compact
	Auto-Dilution	**Manual Dilution**	**Manual Dilution**
Best Case	99.63%	99.63%	100%
Worst Case	99.26%	99.26%	98.89%

The combined reproducibility results for all three sites were acceptable.

b. *Linearity/assay reportable range:*

Not applicable

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

Inoculum Density Control
The DensiCHEK Plus was used to standardize the inoculum to a 0.5 McFarland standard. The instrument was standardized daily with all results recorded at each site. Calibration values were within the expected range.

Purity Check
A purity check of all organisms was performed on the dilution tube used to prepare the VITEK 2 card inoculum. Only those cultures that were pure were evaluated in the study.

Growth Failure Rate
There were ten isolates that failed to grow in the VITEK 2 card in the clinical study. Complete test results were available for 980 isolates from a total of 990 clinical isolates. The growth failure rate was 1.0% and was acceptable.

A challenge set of 93 isolates was evaluated at one site. All 93 challenge organisms grew in the VITEK 2 GN card with Ceftazidime/Avibactam using both the auto-dilution and manual dilution methods for the VITEK 2 and manual inoculation for the VITEK 2 Compact System.

A total of 1073 VITEK 2 AST results were available.

Quality Control (QC) Testing
The FDA/CLSI recommended QC organisms (*E. coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *K. pneumoniae pneumoniae* ATCC 700603) were tested using both the VITEK 2 card and the reference method at each site. Both the automatic dilution and manual dilution methods were used for the VITEK 2 and the manual dilution method was used for the VITEK 2 Compact.

As shown in Table 3, both the auto-dilution and the manual dilution methods for VITEK 2 and the manual dilution for VITEK 2 Compact were within the expected range >95% of the time.

Table 3: Quality Control Summary Results for VITEK 2 (Auto-Dilution and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Ceftazidime/ Avibactam		VITEK 2				VITEK 2 Compact Manual Dilution	
		Auto-Dilution		Manual Dilution			
Organism	Conc. (µg/mL)	Reference	Test	Reference	Test	Reference	Test
E. coli ATCC 25922 FDA/CLSI Expected Range 0.06 – 0.5µg/mL (VITEK 2: ≤0.12-0.5µg/mL)	≤0.015625						
	0.03125						
	0.0625	113		62		62	
	≤ 0.12 **	137	112	74	87	75	103
	0.25	7	146	4	23	4	38
	0.5						
	1	1					
	2						
	≥4						
E. coli ATCC 35218 FDA/CLSI Expected Range 0.03-0.12µg/mL (VITEK 2: ≤0.12µg/mL)	≤0.015625						
	0.03125	41		13		13	
	0.0625	204		119		119	
	≤ 0.12 **	8	252	4	135	4	136
	0.25		1		1		
	0.5						
	1						
	2						
	≥4						
K. pneumoniae pneumoniae ATCC 700603 # Expected Range 0.025- 2µg/mL	≤0.015625						
	0.03125						
	0.0625						
	0.12						1
	0.25	64		18		16	
	0.5	156	258	103	142	103	139
	1	39	1	21		21	
	2		1	1	1	1	1
	≥4						
P. aeruginosa ATCC 27853 Expected Range 0.5 – 4 µg/mL	≤0.0625						
	0.12						
	0.25						
	0.5						
	1	1	8	107	11	107	9
	2	196	244	26	124	26	124
	4	50		3		3	
	8	6					
	16		1		1		3
	32						
	≥64						

* MIC for ceftazidime in the presence of a fixed concentration of 4 µg/mL of avibactam

** The lowest dilution of the VITEK 2 Ceftazidime/Avibactam MIC range is ≤0.12µg/mL. Obtaining this value was considered an indicator that the quality control test results were acceptable.

K. pneumoniae ATCC 700603 should be tested against Ceftazidime/Avibactam and Ceftazidime alone to confirm the activity of Avibactam in the combination and to ensure that the plasmid encoding the beta-lactamase has not been lost in this strain. The acceptable range for Ceftazidime alone is greater than16 µg/mL.

The FDA/CLSI Ceftazidime/Avibactam expected ranges for *E. coli* ATCC 25922 and *E. coli* ATCC 35218 are 0.06 – 0.5 and 0.03 – 0.12µg/mL respectively. However, the VITEK 2 MIC reporting range is ≤0.12 – ≥16 µg/mL (MIC results: ≤0.12, 0.25, 0.5, 1, 2, 4, 8, ≥16 µg/mL). The VITEK 2 systems do not provide results lower than 0.12 µg/mL; therefore, all results for *E. coli* ATCC 35218 and the lower range value for *E. coli* ATCC 25922 are off scale. The quality control test results were considered acceptable for *E. coli* ATCC 25922 and *E. coli* ATCC 35218 when the MIC value of ≤0.12 µg/mL was obtained for these organisms by the VITEK 2 system.

bioMérieux includes the FDA/CLSI broth microdilution expected range in the labeling when the VITEK 2 system range is not aligned with that of the FDA/CLSI range. The additional information is acceptable.

In addition*, K. pneumoniae* ATCC 700603 is recommended to test against ceftazidime alone to ensure the presence of the plasmid encoding beta-lactamase when testing this beta-lactam/beta-lactamase inhibitor combination, ceftazidime/avibactam. The acceptable result for ceftazidime alone is greater than 16µg/mL. The footnote below is added to the QC section of the Package Insert for VITEK 2 AST-GN Ceftazidime/Avibactam:

> *K. pneumoniae ATCC 700603 should be tested against Ceftazidime/Avibactam and Ceftazidime alone to confirm the activity of Avibactam in the combination and to ensure that the plasmid encoding the beta-lactamase has not been lost in this strain. The acceptable range for Ceftazidime alone is greater than16 µg/mL.*

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:

Results obtained with the bioMérieux VITEK 2 AST-Gram Negative card with Ceftazidime/Avibactam were compared to results obtained with the CLSI broth microdilution reference panel. The following concentrations of Ceftazidime/Avibactam are contained in the VITEK 2 AST-GN test card: 0.06/4,

0.25/4, 1/4, 4/4, and 8/4µg/mL (equivalent standard method concentration by efficacy in µg/mL). However, the reporting range is ≤ 0.12 – ≥16 µg/mL for *Enterobacteriaceae* and ≤ 0.25 – ≥16 µg/mL for *Pseudomonas aeruginosa*. The reference panel contained two-fold serial dilutions with a range of ≤ 0.0156 to ≥128 µg/mL. The testing conditions for the reference method consisted of the following:

- Medium – Mueller Hinton broth with appropriate dilutions of antimicrobial solution added
- Inoculum – Direct colony suspension
- Incubation – 35°C ambient air incubator; 16-20 hours

All test inocula used for the evaluation of VITEK 2 AST-GN Ceftazidime/Avibactam and the reference method were standardized using the DensiCHEK Plus instrument. The cards were inoculated with each test organism by auto-dilution for reading by the VITEK 2 System and by manual dilution for reading on the VITEK 2 and VITEK 2 Compact Systems. Reference broth microdilution panels were inoculated in adherence with CLSI document, M07-A10.

A total of 990 clinical isolates were evaluated at three sites with VITEK 2 AST – Gram Negative cards inoculated by automatic dilution and interpreted using the VITEK 2 instrument. There were ten isolates that did not grow in the studies. The no growth rate was 0.1% (10/990). Most isolates were recently isolated from clinical specimen (885 isolates, 89.4%). The remainder were stock isolates (105 isolates, 10.6%).

A total of 93 challenge organisms (47 *Enterobacteriaceae* and 46 *P. aeruginosa*) were evaluated at one site. The challenge set was tested with the auto-dilution and manual dilution options of the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System. Overall performance of the clinical and challenge organisms by auto-dilution is shown in Table 4.1.

Table 4.1: Performance [‡] of Clinical and Challenge Isolates, VITEK 2 Auto-Dilution Method

Ceftazidime/ Avibactam	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Maj	Vmj
***Enterobacteriaceae* ≤8 (Susceptible), --, ≥16 (Resistant)**											
Clinical	819	770	94.0	265	216	81.5	813	99.3	10	6	0
Challenge	47	46	97.9	20	19	95.0	46	97.9	27	1	0
Combined	**866**	**816**	**94.2**	**285**	**235**	**82.5**	**859**	**99.2**	**37**	**7** (0.8%)	**0**
***Pseudomonas aeruginosa* ≤8 (Susceptible), --, ≥16 (Resistant)**											
Clinical	161	152	94.4	145	136	93.8	154	95.7	10	7	0
Challenge	46	46	100	18	18	100	46	100	28	0	0
Combined	**207**	**198**	**95.7**	**163**	**154**	**94.5**	**200**	**96.6**	**38**	**7** (4.1%)	**0**
Enterobacteriaceae* + *Pseudomonas aeruginosa											
Clinical	980	922	94.1	410	352	85.9	967	98.7	20	13	0
Challenge	93	92	98.9	38	37	97.4	92	98.9	55	1	0
Combined	**1073**	**1014**	**94.5**	**448**	**389**	**86.8**	**1059**	**98.7**	**75**	**14** [†] **(1.4%)**	**0**

[†] The overall categorical major error rate for *Enterobacteriaceae and Pseudomonas aeruginosa* combined was 1.4% (14/998). Nine (9) major errors were one dilution apart from the reference method and as such fall within essential agreement. Based on the essential agreement, and the lack of an intermediate breakpoint for Ceftazidime/Avibactam, the adjusted categorical major error rate is 0.5% (5/998).

[‡]**EA** – Essential Agreement (+/- 1 doubling dilution)
CA – Category Agreement
EVAL – Evaluable isolates
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 VITEK 2 test card within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the VITEK 2 test card 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 VITEK 2 test card.

The overall performance using the auto-dilution method for the VITEK 2 System demonstrated an essential agreement of 94.5% and an overall category agreement of 98.7%. The major discrepancy rate was acceptable at 1.4%. However, due to the lack of intermediate category, the maj discrepancy rate was adjusted and was described in a footnote:

> *The overall categorical major error rate for Enterobacteriaceae and Pseudomonas aeruginosa combined was 1.4% (14/998). Nine (9) major errors were one dilution apart from the reference method and as such fall within essential agreement. Based on the essential agreement, and the lack of an intermediate breakpoint for Ceftazidime/Avibactam, the adjusted categorical major error rate is 0.5% (5/998).*

***Pseudomonas aeruginosa* (Reporting range: ≤0.25/4 – ≥16/4 µg/mL)**

When *P. aeruginosa* data was analyzed separately, it was observed that the major discrepancy rate for this organism was 4.1% (7/169) and did not meet the acceptance criterion. Due to the lack of "intermediate" interpretation category, adjusted major discrepancy rate was calculated taking into consideration the MIC values were within essential agreement compared to reference MIC. Of the seven maj discrepancies, five

were within essential agreement [i.e. VITEK 2: ≥16 (R), Reference: 8 (S)] which would have been considered minor discrepancies if there was an "intermediate" interpretative category for *P. aeruginosa*. The adjusted major discrepancy rate was 1.2% (2/169) which met the acceptance criterion.

The adjusted *P. aeruginosa* performance is noted in Table 4.2 below.

Table 4.2: Adjusted Major Discrepancy Performance of *P. aeruginosa* Due to the Lack of an Intermediate Category (VITEK 2 Auto-Dilution Method)

Ceftazidime/ Avibactam	Susceptible #	Major Discrepancies	
		#	Rate
Before Adjustment	169	7	4.1%
After Adjustment	169	2 †	1.2%

† Five (5) *P. aeruginosa* isolates were within essential agreement when compared to the reference method

The original *P. aeruginosa* performance with seven major discrepancies was mitigated by adding a limitation to address the need for repeat testing *P. aeruginosa* by alternative/reference methods when the VITEK 2 Systems MIC is ≥16µg/mL. The limitation is noted below:

> *Although within Essential Agreement when compared to the reference method, errors (major and/or very major) were observed due to the lack of intermediate category. Testing should be repeated using an alternative testing/reference method prior to reporting results for the following antibiotic/organism(s):*
> - *Ceftazidime/Avibactam: Pseudomonas aeruginosa when the VITEK 2 MIC is ≥16µg/mL due to observed major discrepancies (4.1%), with an adjusted categorical major error rate of 1.2%."*

For implementation of the repeat testing limitation, bioMerieux indicated that they will issue a customer communication requesting VITEK 2 users to create a custom BioART rule in the VITEK 2 System software. Implementation of an indication for use BioART rule for a U.S. customer will prevent the user from generating a result when using the AST-GN Ceftazidime/Avibactam test for *Pseudomonas aeruginosa.*

The indication for use and limitation BioART rule will be pre-defined in the VITEK 2 System software in the next software update.

MIC Trends:

The claimed *Pseudomonas aeruginosa* and *Enterobacteriaceae* organisms were also evaluated for trending. This trending calculation takes into account MIC values that are determined to be ≤1 and ≥1 doubling dilutions compared to the reference method irrespective whether the device MIC values are on-scale or not. The trending analysis is shown in Table 4.3 below.

Table 4.3: Trending Analysis of Evaluable Clinical and Challenge Results for *P. aeruginosa* and *Enterobacteriaceae*

Ceftazidime/ Avibactam ≤ 1.25 – ≥ 16µg/mL	Total [a] (Total # Tested)	Difference in MIC as Compared to the CLSI Reference Method				
		≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
P. aeruginosa + *Enterobacteriaceae*	508/1073	15	75	155 (30.51%)	209	54
		90 (17.72%) [b] 95% CI (14.64% to 21.28%)			263 (51.77%) [b] 95% CI (47.43% to 56.09%)	
P. aeruginosa	168 (207)	0	12	69 (41.07%)	78	9
		12 (7.14%) [c] 95% CI (4.13% to 12.07%)			87(51.79%) [c] 95% CI (44.27% to 59.22%)	

[a] Total number of evaluable results for trending analysis

[b] Difference between isolates trending higher and isolates trending lower for *Enterobacteriaceae* and *P. aeruginosa*: 34.06%; 95% CI (28.44% to 39.55%)

[c] Difference between isolates trending higher and isolates trending lower for *P. aeruginosa*: 44.64%; 95% CI (35.66% to 52.66%)

A trend towards higher MIC was observed with *Enterobacteriaceae* and *P. aeruginosa* isolates when compared to the CLSI broth microdilution reference method. This trending and the potential for occurrence of major discrepancies for Ceftazidime/Avibactam when testing clinical and challenge isolate results with the VITEK 2 GN Ceftazidime/Avibactam was addressed by adding the following footnote to the performance table for Ceftazidime/Avibactam in the device labeling (Table 127: Performance Characteristics for Gram-Negative Antimicrobial Susceptibility Testing, VITEK 2 Product Information Manual).

> *VITEK 2 Ceftazidime/Avibactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing Enterobacteriaceae* and *Pseudomonas aeruginosa compared to the reference broth micro-dilution.*

Challenge Data – Auto and Manual Dilution:

The challenge set of 93 isolates (47 *Enterobacteriaceae* and 46 *Pseudomonas aeruginosa*) was evaluated at one site. The challenge set was tested with both the auto-dilution and manual dilution options of the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System.

Overall performance is shown in Table 5.

Table 5: Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact

Ceftazidime/ Avibactam	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Maj	Vmj
VITEK 2											
Auto-dilution	93	92	98.9	38	37	97.4	92	98.9	55	1	0
Manual Dilution	93	92	98.9	38	37	97.4	92	98.9	55	1	0
VITEK 2 Compact											
Manual Dilution	93	92	98.9	38	37	97.4	92	98.9	55	1	0

The performance of the challenge isolates using the VITEK 2 Ceftazidime/Avibactam test on both the VITEK 2 and VITEK 2 Compact Systems was acceptable.

Enzyme Group Characterization/Resistance Markers Information

Enterobacteriaceae with beta-lactamases were included in the ceftazidime/avibactam comparative studies. They were KPC (6), CTX-M (4), TEM (11), SHV (12) and plasmid mediated AmpC (4). The *Enterobacteriaceae* were *Klebsiella pneumoniae, E. coli,* and *Enterobacter cloacae.* The study showed susceptibility to Ceftazidime/Avibactam with VITEK2 MIC values range from 0.5/4 to 2/4 µg/mL.

Additionally, seven *P. aeruginosa* with beta-lactamases AmpC variants PDC (7), KPC (1), GES (1), VEB (1), and outer membrane porin loss OprD (7) were tested. Two isolates demonstrated resistance of ≥16/4 µg/mL and five isolates showed susceptibility ranging from 2/4 to 8/4 µg/mL. The following footnote was added to the ceftazidime/avibactam labeling regarding other resistance markers and enzyme characterization:

- *Enzyme group characterization was not available for the following organisms at the time of comparative testing, and therefore the performance of the AST card with Ceftazidime/Avibactam is unknown: Enterobacteriaceae (OXA, metallo-beta-lactamases); Pseudomonas aeruginosa (metallo-beta-lactamases).*

- *Ceftazidime/Avibactam is not active against bacteria that produce metallo beta-lactamase enzymes and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations.*

b. Matrix comparison:

Not applicable

3. Clinical studies:

   Not applicable

4. Clinical cut-off**:**

   Not applicable

5. Expected values/Reference range:

Table 6: Interpretive Criteria for Ceftazidime/Avibactam (FDA Drug Label)

Organism	FDA Interpretive Criteria for Ceftazidime/Avibactam MIC (µg/mL)		
	S	I	R
Enterobacteriaceae *Pseudomonas aeruginosa*	≤8/4	--	≥16/4

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