510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193299

B Applicant

bioMérieux, Inc.

C Proprietary and Established Names

VITEK 2 AST-Gram Negative Ceftazidime (≤0.5 - ≥32 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LON, LTT, LTW	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:

To obtain a substantial equivalence determination for ceftazidime for testing of Gram-negative bacilli on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

B Measurand:

Ceftazidime ≤0.5 – ≥32 µg/mL

C Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test

III Intended Use/Indications for Use:

A Intended Use(s):

The VITEK 2 Gram-Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed.

B Indication(s) for Use:

VITEK 2 AST-Gram Negative Ceftazidime 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 is a quantitative test. Ceftazidime has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

Active *in vitro* and in clinical infections:
Citrobacter species
Enterobacter species
Escherichia coli
Klebsiella species
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia species

In vitro data are available, but clinical significance is unknown:
Acinetobacter species
Citrobacter koseri (formally *Citrobacter diversus*)
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species
Shigella species
Yersinia enterocolitica

The VITEK 2 Gram-Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed.

C Special Conditions for Use Statement(s):

- Rx - For Prescription Use Only

- The lack of an intermediate category has shown very major discrepancies when compared to the reference method. Testing should be repeated using an alternative method prior to reporting results for the following antibiotic/organism combination(s):
  Ceftazidime: *Pseudomonas aeruginosa* when the VITEK 2 MIC is 8 µg/ml.

- Perform an alternative method of testing prior to reporting for the following antibiotic / organism combination(s):
  Ceftazidime: *Morganella morganii*

- The ability of the AST card to detect resistance with the following combination(s) is unknown because an insufficient number of resistant strains were available at the time of comparative testing:
  Ceftazidime: *Citrobacter koseri, Yersinia enterocolitica*

D Special Instrument Requirements:

VITEK 2 and VITEK 2 Compact Systems using VITEK 2 Systems 9.02 software or later versions

IV Device/System Characteristics:

A 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 (or allow operator to manually) 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. 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 antimicrobial 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-Gram Negative Ceftazidime has the following concentrations in the card: 1, 2, 4, 8 and 32 μg/mL (equivalent standard method concentration by efficacy in μg/mL). The ceftazidime MIC result range for the VITEK 2 is ≤0.5 to ≥32 μg/mL. For all species, the VITEK 2 system is capable of reporting the following MIC results: ≤0.5, 1, 2, 4, 8, 16 and ≥32 μg/mL for the AST-Gram Negative Ceftazidime test.

B Principle of Operation:

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 use 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 determine 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):
VITEK 2 AST-Gram Negative Eravacycline (≤0.12 - ≥4µg/mL)

B Predicate 510(k) Number(s):
K191766

C Comparison with Predicate(s):

Table 1. Device Comparison with Predicate

Device & Predicate Device(s):	**Device: K193299**	**Predicate: K191766**
Device Trade Name	Vitek 2 AST-Gram Negative Ceftazidime (≤0.5 – ≥32 µg/mL)	Vitek 2 AST-Gram Negative Eravacycline (≤0.12 – ≥4 µg/mL)
General Device Characteristic Similarities		
Intended Use	The VITEK 2 Gram-Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed.	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
General Device Characteristic Differences		
Antimicrobial Agent	Ceftazidime	Eravacycline
Antimicrobial Concentration	1, 2, 4, 8 and 32 µg/mL	0.25, 1, 2 and 4 µg/mL
Reporting Range	≤0.5 to ≥32 µg/mL	≤0.12 to ≥4 µg/mL
Indicated Organisms	*Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Serratia* species, *Acinetobacter* species, *Citrobacter koseri (formally Citrobacter diversus)*, *Citrobacter*	*Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Klebsiella (Enterobacter) aerogenes*

Device & Predicate Device(s):	Device: K193299	Predicate: K191766
	freundii, *Providencia* species *(including Providencia rettgeri)*, *Salmonella* species, *Shigella* species, *Yersinia enterocolitica*	

VI Standards/Guidance Documents Referenced:

- Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.
- CLSI M07, 10th ed., "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard, 2015".
- CLSI M100, 29th ed., "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Ninth Informational Supplement, January 2019".

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Reproducibility testing for the VITEK 2 AST-GN card with Ceftazidime was conducted at three external clinical sites using a panel of ten Gram-negative bacilli consistent with the indications for use (i.e., four *Pseudomonas aeruginosa*, three *Enterobacter* spp., two *Serratia marcescens* and one *Klebsiella pneumoniae pneumoniae*). Each isolate was tested in triplicate over three days for a total of 270 data points. Inocula were prepared using both the auto-dilution and manual dilution methods for testing in the VITEK 2 System. In addition, inocula were prepared by the manual dilution method for use with the VITEK 2 Compact. The mode or median of MIC values was determined for each isolate and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode/median MIC value. 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 summarized in **Table 2**.

Table 2. Reproducibility of VITEK 2 AST-GN with Ceftazidime

	VITEK 2		VITEK 2 Compact
	Auto-Dilution	Manual Dilution	Manual Dilution
Best Case	262/270 (97.0%)	261/270 (96.7%)	263/270 (97.4%)
Worst Case	250/270 (92.6%)	247/270 (91.5%)	254/270 (94.1%)

All reproducibility performance results were considered acceptable.

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 (QC) Testing:
The CLSI recommended QC strains, namely *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested a sufficient number of times (i.e., at least 20/site) at each testing site using both the VITEK 2 card and broth microdilution (BMD) reference methods. 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. The results for all sites combined are summarized in **Table 3**.

The quality control results were within the expected results range > 95% of the time which is acceptable.

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

Organism	VITEK 2 Result Range[1] (µg/mL)	BMD Result Range (µg/mL)	VITEK 2 Auto-Dilution	BMD	VITEK 2 Manual Dilution	BMD	VITEK 2 Compact Manual Dilution	BMD
E. coli ATCC 25922 Expected Result: 0.06 – 0.5 µg/mL		≤0.03						
		0.06						
		0.125		153		118		114
		0.25		110		65		65
	≤ 0.5	0.5	266	3	185	2	181	2
	1	1						
	2	2						
	4	4						
	8	8						
	16	16						
	≥ 32	32						
		64						
		≥128						
P. aeruginosa ATCC 27853 Expected Result: 1 - 4 µg/mL		≤0.03						
		0.06						
		0.125						
		0.25						
	≤ 0.5	0.5						
	1	1		181		126		125
	2	2	267	84	185	57	182	55
	4	4		1		1		1

Organism	VITEK 2 Result Range[1] (µg/mL)	BMD Result Range (µg/mL)	VITEK 2 Auto-Dilution	BMD	VITEK 2 Manual Dilution	BMD	VITEK 2 Compact Manual Dilution	BMD
	8	8		1[2]		1[2]		1[2]
	16	16						
	≥ 32	32						
		64						
		≥128						

[1] Does not include the full CLSI/FDA-recommended dilution range for QC testing. For *E. coli*, an in-range VITEK result will be ≤ the lowest dilution on the card (i.e., ≤ 0.5 µg/mL).

[2] Two replicates of this organism were tested; one result was out of range. Since the results for the other replicate and the other QC organisms were within the acceptable range, the reference results were accepted and testing was not repeated. QC results were within the expected range on the next testing day.

Inoculum Density Check:
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:
A total of 981 clinical isolates were evaluated. A total of 977 organisms grew in the VITEK 2 AST-Gram Negative Ceftazidime test using the auto-dilution method which is acceptable (<10% growth failure).

A total of 118 challenge isolates were evaluated at one site. All 118 challenge organisms grew in the VITEK 2 AST-Gram Negative Ceftazidime test using both the auto-dilution and manual dilution methods for the VITEK 2 and manual dilution method for the VITEK 2 Compact.

A total of four isolates did not grow in the VITEK 2 AST-Gram Negative Ceftazidime test so complete test results are available for 1095 isolates.

6. Detection Limit:

   Not applicable

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with the Reference Method

Testing of ceftazidime on the VITEK 2 AST-Gram Negative card was performed at three external sites and one internal site. There were 981 clinical isolates and 118 challenge isolates tested for a total of 1099 isolates. Results obtained with the VITEK 2 AST-Gram Negative card with ceftazidime were compared to results obtained with the CLSI broth microdilution reference panel. The MIC result range for the VITEK 2 AST-Gram Negative Ceftazidime is ≤0.5 to ≥32 µg/mL for all species. The reference panel contained two-fold serial dilutions with a range of ≤0.0313 to ≥256 µg/mL. The testing conditions for the reference method consisted of the following:

- Medium – Cation Adjusted Mueller Hinton broth
- Inoculum – Direct colony suspension
- Incubation – 35°C; 16-20 hours

The VITEK 2 AST cards were inoculated with test organisms using the auto-dilution method (VITEK 2) and using the manual dilution method (VITEK 2 and VITEK 2 Compact). All test inocula used for the VITEK 2 AST cards and the reference method were standardized using the DensiCHEK Plus instrument.

A total of 981 clinical isolates were evaluated: 67.9% were considered contemporary isolates (isolated from clinical specimens and tested within six months) and 32.1% were stock isolates. Four isolates did not grow in the VITEK 2 AST-Gram Negative Ceftazidime test so complete test results are available for 977 clinical isolates: 968 isolates from indicated species (25 *A. baumannii,* 13 *A. baumannii* complex, 1 *A. lwoffii,* 1 *Acinetobacter* spp., 1 *C. amalonaticus,* 2 *C. braakii,* 12 *C. freundii,* 3 *C. koseri,* 1 *E. amnigenus,* 1 *E. asburiae,* 27 *E. cloacae cloacae,* 21 *E. cloacae* complex, 156 *E. coli,* 16 *K. aerogenes,* 27 *K. oxytoca,* 1 *K. pneumoniae pneumoniae,* 109 *K. pneumoniae,* 54 *P. mirabilis,* 13 *P. vulgaris,* 7 *P. rettgeri,* 5 *P. stuartii,* 403 *P. aeruginosa,* 13 *Salmonella* spp., 27 *S. marcescens,* 1 *S. rubidaea,* 3 *S. boydii,* 3 *S. dysenteriae,* 5 *S. flexneri,* 4 *S. sonnei* and 13 *Y. enterocolitica*) and 9 isolates from non-indicated species (3 *B. cepacia,* 3 *H. alvei,* 1 *P. agglomerans,* 2 *R. planticola).* The clinical isolates were tested with the auto-dilution option of the VITEK 2.

A total of 118 challenge isolates (10 *A. baumannii,* 4 *A. baumannii* complex, 1 *A. calcoaceticus,* 1 *A. johnsonii,* 1 *A. lwoffii,* 1 *Acinetobacter* spp., 3 *C. freundii,* 3 *C. koseri,* 4 *E. cloacae cloacae,* 20 *E. coli,* 9 *K. aerogenes,* 2 *K. oxytoca,* 6 *K. pneumoniae pneumoniae,* 9 *P. mirabilis,* 2 *P. vulgaris,* 2 *P. rettgeri,* 2 *P. stuartii,* 20 *P. aeruginosa,* 2 *Salmonella enterica arizonae,* 8 *S. marcescens,* 1 *S. odorifera,* 2 *S. boydii,* 3 *S. flexneri* and 2 *Y. enterocolitica*) were evaluated at one site. The challenge set was tested with the auto-dilution and manual dilution options of the VITEK 2 and with the manual dilution method on the VITEK 2 Compact.

At the time of comparative testing, resistant isolates were not available for *Citrobacter koseri* and *Yersinia enterocolitica*. The following statement is included in the *Limitations* section of the device labeling:

> *The ability of the AST card to detect resistant strains with the following combination(s) is unknown because an insufficient number of resistant strains were available at the time of comparative testing.*
>
> *Ceftazidime: Citrobacter koseri, Yersinia enterocolitica*

Clinical and Challenge Data –VITEK 2 Auto-Dilution

The results obtained using the auto-dilution method of the VITEK 2 from the 1095 total isolates (977 clinical isolates and 118 challenge isolates) are summarized in **Table 4.**

Table 4. Performance of All Clinical and Challenge Isolates: VITEK 2 *Auto-Dilution*

Organism Type	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	min	maj	vmj
***Acinetobacter* spp.**												
Clinical	40	38	95.0	24	22	91.7	36	90.0	17	4	0	0
Challenge	18	16	88.9	10	8	80.0	16	88.9	8	2	0	0
Combined	**58**	**54**	**93.1**	**34**	**30**	**88.2**	**52**	**89.7**	**25**	**6**	**0**	**0**
***Enterobacteriaceae* [1]**												
Clinical	525	514	97.9	25	14	58.3	514	98.3	44	10	1	0
Challenge	80	78	97.5	6	4	66.7	77	96.3	2	1	2	0
Combined	**605**	**592**	**97.9**	**31**	**18**	**58.1**	**591**	**97.7**	**46**	**11**	**3**	**0**
Pseudomonas aeruginosa												
Clinical	403	380	94.3	259	236	91.1	391	97.0	155	N/A	3	9
Challenge	20	20	100	18	18	100	20	100	0	N/A	0	0
Combined	**423**	**400**	**94.6**	**277**	**254**	**91.7**	**411**	**97.2**	**155**	**N/A**	**3**	**9**

[1] Only includes data for *Enterobacteriaceae* species indicated for VITEK 2 Ceftazidime.

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
min – minor errors
maj – major errors
vmj – very major errors
N/A – Not applicable due to the lack of an intermediate interpretive criterion for ceftazidime with *P. aeruginosa*

When using the auto-dilution method of the VITEK 2, the overall performance of *Acinetobacter* spp. is acceptable with an EA of 93.1% and a CA of 89.7%. There were no major or very major errors. The overall performance with all *Enterobacteriaceae* is acceptable with an EA of 97.9% and a CA of 97.7%. There were three major errors (3/559 = 0.5%) and no very major errors. The overall performance of *Pseudomonas aeruginosa* is acceptable with an EA of 94.6% and a CA of 97.2%. There were three major (3/268 = 1.1%) and nine (9/155 = 5.8%) very major errors; seven of the nine very major errors had MIC values of 8 µg/mL. This is addressed as a limitation statement in the device labeling:

> *The lack of an intermediate category has shown very major discrepancies when compared to the reference method. Testing should be repeated using an alternative method prior to reporting results for the following antibiotic/organism combination(s):*
>
> *Ceftazidime: Pseudomonas aeruginosa when the VITEK 2 MIC is 8 µg/ml.*

Due to the lack of an intermediate interpretive criteria for ceftazidime with *P. aeruginosa*, further analysis of the errors is performed and adjustments are made by considering the MIC values where the errors occurred. Two of the three major errors had an MIC value that was one doubling dilution from the reference and thus in essential agreement. Therefore, the adjusted number of major errors is reduced to 1 (1/268 = 0.4%). Five of the nine very major errors had an MIC value that was one doubling dilution from the reference and thus in

essential agreement. Therefore, the adjusted number of very major errors is reduced to four (4/155 = 2.6%). In addition, seven of the nine very major errors had MIC values of 8 µg/mL. To describe the very major errors, these results are addressed as a footnote to the performance table in the device labeling:

The overall categorical very major error rate for ceftazidime when testing Pseudomonas aeruginosa with the VITEK 2 system was 5.8% (9/155). The MIC values of five of the nine very major errors were one doubling dilution from the MIC value obtained from the reference method. Based on the essential agreement and lack of an intermediate breakpoint for ceftazidime with P. aeruginosa, the adjusted very major error rate for P. aeruginosa is 2.6% (4/155). Seven of the nine very major errors had MIC values of 8 µg/mL; therefore, alternative testing is required prior to reporting results for P. aeruginosa when the VITEK 2 MIC value is 8 µg/mL.

Challenge Data –VITEK 2 and VITEK 2 Compact Manual Dilution

The 118 challenge isolates were also evaluated at one site with the manual dilution options of the VITEK 2 and VITEK 2 Compact systems (summarized in **Table 5**).

Table 5. Performance of Challenge Isolates: VITEK 2 and VITEK 2 Compact *Manual Dilution*

System	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	min	maj	vmj
***Acinetobacter* spp.**												
VITEK 2	18	16	88.9	10	8	80.0	16	88.9	8	2	0	0
VITEK 2 Compact	18	16	88.9	10	8	80.0	16	88.9	8	2	0	0
Enterobacteriaceae												
VITEK 2	80	80	100	4	4	100	79	98.8	2	1	0	0
VITEK 2 Compact	80	80	100	4	4	100	79	98.8	2	1	0	0
Pseudomonas aeruginosa												
VITEK 2	20	20	100	18	18	100	20	100	0	0	0	0
VITEK 2 Compact	20	20	100	18	18	100	20	100	0	0	0	0

When using the manual dilution method of the VITEK 2 and VITEK2 Compact, the overall performance of all *Acinetobacter* spp. challenge isolates had an EA and CA of 88.9%. This performance is less than the 90% performance criteria outlined in the AST Special Controls guidance document, likely due to the limited number of challenge isolates available for testing. Of the 18 challenge isolates tested, 8 isolates had MIC values that were not evaluable for EA. Of the 10 evaluable MIC values, there were no major or very major errors. This is addressed in the following footnote to the performance table in the device labeling:

A limited number of Acinetobacter isolates were available for testing with the manual dilution. Of the 18 isolates tested, 8 had MIC values that were not evaluable for essential agreement. Of the 10 evaluable MIC values, there were 2 minor categorical errors that were not in essential agreement.

When using the manual dilution method of the VITEK 2 and VITEK2 Compact, the overall performance of all *Enterobacteriaceae* challenge isolates is acceptable with an EA of 100% and a CA of 98.8%. There were no major or very major errors. Overall performance of *P. aeruginosa* challenge isolates with either instrument is acceptable with an EA and CA of 100%. There were no major or very major errors.

Resistance Mechanism Characterization
Challenge isolates of *Enterobacteriaceae* and *P. aeruginosa* harboring various molecular mechanisms of resistance noted in the FDA drug label were tested with ceftazidime. The following resistance mechanisms were evaluated: β-lactamases (OXA, SHV, TEM, AMPC and others).

MIC Trends
A trending analysis was conducted using the combined data (clinical and challenge) obtained from the VITEK 2 auto-dilution method for each indicated organism species and group. This trending calculation analyzes device MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method. MIC values that are off-scale for both the reference and device are not considered in the trending analysis.

Trending results were stratified by species to determine if species-related trends were observed (**Table 6**). Species for which the difference between the percentage of isolates with higher or lower MIC values was ≥30% with a statistically significant confidence interval were considered to have evidence of trending.

Table 6. Trending by Species (Clinical and Challenge Isolates)

VITEK 2 Auto-Dilution						
Organism	**Total Evaluable for Trending**	**≥1 dil. Lower # (%)**	**Exact # (%)**	**≥1 dil. Higher # (%)**	**Percent Difference (95% CI)**	**Trending Noted**
***Acinetobacter* spp[1]**	34	7 (20.59)	12 (35.29)	15 (44.12)	23.53 (1.28 to 42.89)	No
Pseudomonas aeruginosa	289	48 (16.61)	153 (52.94)	88 (30.45)	13.84 (6.95 to 20.58)	No
Enterobacteriaceae	45	21 (46.67)	7 (15.5)	17 (37.78)	-8.89 (-27.96 to 11.15)	No
Citrobacter spp[2]	2	0	1 (50.0)	1 (50.0)	50.00 (-27.26 to 90.55)	No
Enterobacter spp[3]	8	3 (37.50)	2 (25.00)	3 (37.50)	0 (-39.83 to 39.83)	No
Escherichia coli	9	2 (22.22)	4 (44.44)	3 (33.33)	11.11 (-27.75 to 46.17)	No
Klebsiella spp[4]	11	7 (63.64)	0	4 (36.36)	-27.27 (-57.25 to 12.69)	No
Proteus mirabilis	4	1 (25.00)	0	3 (75.00)	50.00 (-13.55 to 78.91)	No
Proteus vulgaris	1	0	0	1 (100)	100 (-12.21 to 100)	No

VITEK 2 Auto-Dilution						
Organism	**Total Evaluable for Trending**	**≥1 dil. Lower # (%)**	**Exact # (%)**	**≥1 dil. Higher # (%)**	**Percent Difference (95% CI)**	**Trending Noted**
Providencia spp[5]	3	1 (33.33)	0	2 (66.67)	33.33 (-31.58 to 71.78)	No
Salmonella spp[6]	0	-	-	-	-	-
Serratia spp[7]	1	1 (100)	0	0	-100 (-100 to 12.21)	No
Shigella spp[8]	0	-	-	-	-	-
Yersinia enterocolitica	7	6 (85.71)	0	1 (14.29)	-71.43 (-88.00 to -19.06)	Yes

[1] *A. baumannii*, A. baumannii* complex*, *A. calcoaceticus*, A. johnsonii*, A. lwoffii*, Acinetobacter* spp.*
[2] *C. freundii*, C. koseri**
[3] *E. amnigenus, E. asburiae, E. cloacae cloacae*, E. cloacae* complex
[4] *K. aerogenes*, K. oxytoca, K. pneumoniae*, K. pneumoniae pneumoniae**
[5] *P. rettgeri*, P. stuartii**
[6] *S. enteritica arizonae, Salmonella* spp
[7] *S. marcescens*, S. odorifera, S. rubidaea*
[8] *S. boydii, S. dysenteriae, S. flexneri, S. sonnei*
*denotes species with MIC results evaluable for trending

A trend toward lower MIC values was observed for *Yersinia enterocolitica*. The following footnote to the performance table is included in the package insert to address the trending observed for VITEK 2 AST-Gram Negative Ceftazidime:

> *VITEK 2 AST-Gram Negative Ceftazidime values tended to be in exact agreement or at least one doubling dilution lower when testing Yersinia enterocolitica compared to the CLSI reference broth microdilution.*

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included in the *Precautions* section of the device labeling to address testing and reporting of non-indicated species:

> *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.*

2. Matrix Comparison:

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):

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The FDA-identified and recognized susceptibility interpretive criteria for ceftazidime are listed in **Table 7**.

Table 7: FDA-Identified and Recognized Interpretive Criteria for Ceftazidime (µg/mL)[a]

Organisms	S	I	R
Acinetobacter spp	≤8	16	≥32
Enterobacteriaceae	≤4	8	≥16
Pseudomonas aeruginosa	≤8	-	≥16

[a]According to FDA STIC Website.

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.

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate the VITEK 2 AST-GN Ceftazidime when revised breakpoints for ceftazidime are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, bioMérieux will update the ceftazidime device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.