510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193567

B Applicant

BioMerieux, Inc.

C Proprietary and Established Names

VITEK 2 AST- Gram Negative Polymyxin B (≤ 0.25 - ≥ 16 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
LTW	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LTT	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain substantial equivalence determination for Polymyxin B for antimicrobial susceptibility testing of *Pseudomonas aeruginosa* on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

B Measurand:

Polymyxin B ≤ 0.25 – ≥ 16 µg/mL

C Type of Test:

An automated quantitative or qualitative antimicrobial susceptibility test for Polymyxin B

III Intended Use/Indications for Use:

A Intended Use(s):

The VITEK 2 Gram-negative Susceptibility Card is intended to 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 Polymyxin B 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 Polymyxin B is a quantitative test.

Polymyxin B 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:

Pseudomonas aeruginosa

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

D Special Instrument Requirements:

VITEK 2 and VITEK 2 Compact Systems using VITEK 2 Systems Version 9.03 Software

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 the 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. The analysis program determines when a well demonstrates growth based on attenuation of light measured by an optical scanner. These data are 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-GN Polymyxin B has the following concentrations in the card: 0.125, 0.5, 2 and 8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The Polymyxin B MIC result range for the VITEK 2 is ≤ 0.25 to ≥ 16 µg/mL for *Pseudomonas aeruginosa*. The VITEK 2 system is capable of reporting the following MIC results: ≤ 0.25, 0.5, 1, 2, 4, 8 and ≥ 16 µg/mL for the AST-Gram Negative Polymyxin B 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 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 Delafloxacin (≤ 0.06 – ≥ 4 µg/mL)

B Predicate 510(k) Number(s):
K183524

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device** K193567	**Predicate** K183524
Device Trade Name	VITEK 2 AST-Gram Negative Polymyxin B (≤ 0.25 – ≥ 16 µg/mL)	VITEK 2 AST-Gram Negative Delafloxacin (≤ 0.06 – ≥ 4 µg/mL)
General Device Characteristic Similarities		
Intended Use	The VITEK 2 Gram-negative Susceptibility Card is	Same

	intended to 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	
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	Saline suspension of 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	Polymyxin B	Delafloxacin
Antimicrobial Concentration	0.125, 0.5, 2 and 8 µg/mL	0.06, 0.25, 0.5, and 2 µg/mL
Reporting Range	≤ 0.25 to ≥ 16 µg/mL	≤ 0.06 to ≥ 4 µg/mL
Indicated Organism(s)	*Pseudomonas aeruginosa*	*Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa*

VI Standards/Guidance Documents Referenced:

1. FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)
2. CLSI M07-A11, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically"; Eleventh Edition (January 2018)
3. CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-ninth Edition (January 2019)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Reproducibility testing was performed on a 10-organism panel at one internal and two external sites according to the FDA AST Guidance document. Each isolate was tested in triplicate over three days for a total of 270 data points. Reproducibility was evaluated for both the automatic and manual dilution methods for preparation of inocula on the VITEK 2 and the VITEK 2 Compact. The mode of MIC values was determined for each isolate, and reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode. All data points were on scale, except for 1 result for the VITEK 2 Automatic Dilution. The reproducibility performance for all three sites was acceptable with a range of 99.63-100% for the various VITEK instruments and card inoculation methods.

2. Linearity:

   N/A

3. Analytical Specificity/Interference:

   N/A

4. Assay Reportable Range:

   N/A

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

   Quality Control (QC) Testing: The CLSI-recommended QC strains, *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested at least 20 times per 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.

   QC results are summarized in **Table 1**. The VITEK 2 card for polymyxin B does not include the full CLSI/FDA-recommended dilution range for QC testing of *E. coli* ATCC 25922. Thus, obtaining a result of ≤ 0.25 µg/mL (lowest dilution on the card) was considered as an indicator that the quality control test results were acceptable. To address this, the sponsor included the following footnote in the *Quality Control* section of the device labeling:

   Does not include the full CLSI/FDA-recommended dilution range for QC testing.

Table 1. QC Results for VITEK 2 (Auto and Manual Dilution), VITEK 2 Compact (Manual Dilution), and Reference Broth Microdilution (BMD) Method

	Result Range (µg/mL)		Result Frequency					
Organism	**VITEK 2 Card**	**BMD**	**Auto-Dilution**	**BMD**	**Manual Dilution**	**BMD**	**Compact Manual Dilution**	**BMD**
E. coli ATCC 25922[1] Expected Result: 0.25 – 2 µg/mL		≤ 0.06						
		0.12						
	≤ 0.25	0.25		25		24		25
	0.5	0.5	126	84	87	55	88	55
	1	1		17		8		8
	2	2						
	4	4						
	≥ 8	8						
		16						
		≥ 32						
P. aeruginosa ATCC 27853 Expected Result: 0.5 – 2 µg/mL		≤ 0.06						
		0.12						
	≤ 0.25	0.25						
	0.5	0.5		41		39		39
	1	1	74	78	83	46	84	45
	2	2	52	7	5	3	3	3
	4	4						
	≥ 8	8						
		16						
		≥ 32						

* The gray shaded boxes denote the recommended dilution range for QC testing

[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., ≤ 0.25)

All QC results were within the expected range 100% of the time. The quality control results are acceptable.

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 304 clinical isolates were evaluated at 3 sites. A total of 295 organisms grew in the VITEK 2 AST-GN Polymyxin B test using the auto-dilution method which is acceptable (< 10% growth failure). A total of 85 challenge isolates were evaluated at one internal site. All 85 challenge organisms grew in the VITEK 2 AST-GN Polymyxin B

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 380 VITEK 2 AST-GN Polymyxin B test results were available.

6. Detection Limit:

N/A

7. Assay Cut-Off:

N/A

B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of Polymyxin B on the VITEK 2 AST-Gram Negative card was performed at three external sites and one internal site.

There were 304 clinical isolates and 85 challenge isolates tested for a total of 389 isolates. Results obtained with the VITEK 2 AST-GN card with Polymyxin B were compared to results obtained with the CLSI broth microdilution reference panel. The MIC result range for the VITEK 2 AST-Gram Negative Polymyxin B is ≤ 0.25 – ≥ 16 μg/mL. The reference panel contained two-fold serial dilutions with a range of ≤ 0.06 to ≥ 64 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 for 16 to 20 hours

The VITEK 2 AST cards were inoculated with test organisms using the auto-dilution method (VITEK 2) and 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 304 clinical *P. aeruginosa* isolates were evaluated. Nine isolates did not grow in the VITEK 2 AST-Gram Negative Polymyxin B test so complete test results were available for 295 isolates: 77.6% (229 isolates) were considered contemporary isolates and 25.4% (75 isolates) were stock isolates. The clinical isolates were tested with the auto-dilution option for the VITEK 2.

A total of 85 challenge *P. aeruginosa* isolates were evaluated at one external site. The challenge set was tested with the auto-dilution and manual dilution options for the VITEK 2 and with the manual dilution method on the VITEK 2 Compact.

Clinical and Challenge Data – VITEK 2 Auto-Dilution

The results obtained using the auto-dilution method for the VITEK 2 from the 380 total tested isolates (295 clinical isolates and 85 challenge isolates) are summarized in **Table 2.**

Table 2. Performance of All Isolates: VITEK 2 Auto-Dilution

Organism Type	Tot	EA N	EA %	Eval. Tot	Eval. EA N	Eval. EA %	CA N	CA %	# R	min	maj	vmj
Clinical	295	276	93.6	293	274	93.5	282	95.6	0	9	4	0
Challenge	85	81	95.3	78	74	94.9	85	100	8	0	0	0
Combined	**380**	**357**	**93.9**	**371**	**348**	**93.8**	**367**	**96.6**	**8**	**9**	**4**	**0**

EA *– Essential Agreement*
CA *– Category Agreement*
Eval *– Evaluable isolates*
R *– Resistant isolates*
min *– minor errors*
maj *– major errors*
vmj *– very major errors*

Overall performance is acceptable with an EA of 93.9% and a CA of 96.6%. As summarized in **Table 2**, there were four major errors (4/371 = 1.1%).

Challenge Data – VITEK 2 and VITEK 2 Compact Manual Dilution

The results obtained using the manual dilution method for the VITEK 2 and VITEK 2 Compact after evaluation of the 85 challenge isolates are summarized in **Table 3.**

Table 3. Performance of Challenge Isolates: VITEK 2 and VITEK 2 Compact Manual Dilution

Organism Type	Tot	EA N	EA %	Eval. Tot	Eval. EA N	Eval. EA %	CA N	CA %	# R	min	maj	vmj
VITEK 2	85	82	96.5	77	74	96.1	84	98.8	8	0	1	0
VITEK 2 Compact	85	81	95.3	77	73	94.8	84	98.8	8	0	1	0

EA *– Essential Agreement*
CA *– Category Agreement*
Eval *– Evaluable isolates*
R *– Resistant*
min *– minor errors*
maj *– major errors*
vmj *– very major errors*

Overall performance of VITEK 2 using the manual dilution method with all challenge isolates is acceptable with an EA of 96.5% and a CA of 98.8%. There was one major error (1/77 = 1.3%).

Overall performance of VITEK 2 Compact using the manual dilution method with all challenge isolates is acceptable with an EA of 95.3% and a CA of 98.8%. There was one major error (1/77 = 1.3%).

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:

> *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.

MIC Trends

A trending analysis was conducted using the combined data (clinical and challenge isolates) obtained from the VITEK 2 auto-dilution method (**Table 4**). 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. A difference between the percentage of isolates with higher or lower MIC values that is ≥ 30% with a statistically significant confidence interval is considered to have evidence of trending.

Table 4. Trending (Clinical and Challenge Isolates)

Organism	Total Evaluable for Trending	≥1 dil. Lower # (%)	Exact # (%)	≥1 dil. Higher # (%)	Percent Difference (95% CI)	Trending Noted
P. aeruginosa	373	82 (22.0%)	188 (50.4%)	103 (27.6%)	5.63% (-0.6 to 11.8%)	No

There is no evidence of significant trending observed.

2. Matrix Comparison:

N/A

C Clinical Studies:

1. Clinical Sensitivity:

N/A

2. Clinical Specificity:

N/A

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

N/A

D Clinical Cut-Off:

N/A

E Expected Values/Reference Range:

The FDA-recognized susceptibility test interpretive criteria for Polymyxin B are listed in **Table 5** according to the FDA STIC website.

Table 5: Susceptibility Test Interpretive Criteria for Polymyxin B (µg/mL)

Organism	S	I	R
Pseudomonas aeruginosa	≤ 2	4	≥ 8

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. The protocol outlined the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate the VITEK 2 AST-GN Polymyxin B when revised breakpoints for Polymyxin B 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 Polymyxin B 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.