510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K202396

B Applicant

bioMérieux, Inc.

C Proprietary and Established Names

VITEK 2 AST-Gram Positive Fosfomycin (≤8 - ≥256 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 a substantial equivalence determination for fosfomycin for testing of *Enterococcus faecalis* on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems.

B Measurand:

Fosfomycin ≤ 8 – ≥ 256 µg/mL for *Enterococcus faecalis*

C Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test.

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
VITEK 2 AST-Gram Positive Fosfomycin is designed for antimicrobial susceptibility testing of Gram positive microorganisms 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 Positive Fosfomycin is a quantitative test. Fosfomycin 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:

Enterococcus faecalis

The VITEK 2 Gram-Positive 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-positive microorganisms 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, VITEK 2 Systems (PC) version 9.04

IV Device/System Characteristics:

A Device Description:

The VITEK 2 AST card is essentially 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 which only contains microbiological culture media is resident on all cards. The remaining wells contain premeasured portions of a specific antibiotic combined with culture media. The bacterial or yeast isolate to be tested is diluted to a standardized concentration with 0.45 – 0.5% saline before being used to rehydrate the antimicrobial medium within the card. The VITEK 2 System automatically fills, seals and places 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. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antibiotic contained on the card.

VITEK 2 AST-GP Fosfomycin has the following concentrations in the card: 8, 16, 32, and 128 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 AST-GP Fosfomycin test is ≤ 8 – ≥ 256 µg/mL for *Enterococcus faecalis*. For all species, the MIC result range indicates that the VITEK 2 system is capable of producing the following MIC results ≤ 8, 16, 32, 64, 128, and ≥ 256 µg/mL for the AST-GP Fosfomycin 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 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.

V *Substantial Equivalence Information:*

A Predicate Device Name(s):
VITEK 2 AST-Gram Positive Dalbavancin (≤ 0.015 - ≥ 1 µg/mL)

B Predicate 510(k) Number(s):
K190616

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device:** K202396	**Predicate:** K190616
Device Trade Name	VITEK 2 AST-GP Fosfomycin (≤ 8 - ≥ 256 µg/mL)	VITEK 2 AST-GP Dalbavancin (≤ 0.015 - ≥ 1 µg/mL)
General Device Characteristic Similarities		
Intended Use/Indications For Use	VITEK 2 AST-Gram Positive Fosfomycin is designed for antimicrobial susceptibility testing of Gram positive microorganisms 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	VITEK 2 AST-Gram Positive Dalbavancin is designed for antimicrobial susceptibility testing of Gram positive microorganisms 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 Positive Fosfomycin is a quantitative test. Fosfomycin 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:** *Enterococcus faecalis* The VITEK 2 Gram-Positive 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-positive microorganisms to antimicrobial agents when used as instructed.	agents. VITEK 2 AST-Gram Positive Dalbavancin is a quantitative test. Dalbavancin 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** *Staphylococcus aureus* (including methicillin-resistant isolates) *Enterococcus faecalis* (vancomycin-susceptible isolates only) *Streptococcus agalactiae* The VITEK 2 Gram-positive Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of *Staphylococcus* spp., *Enterococcus* spp., and *S. agalactiae* 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 microorganisms	Same
Inoculum	Saline suspension of organism	Same
Test Card	Gram Positive (AST-GP) Susceptibility Card	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Analysis Algorithm	Growth pattern analysis	Same
General Device Characteristic Differences		
Antimicrobial Agent	Fosfomycin	Dalbavancin
Concentrations	8, 16, 32, 128	0.0625, 0.125, 0.25, 0.5
Indicated Organisms	*Enterococcus faecalis*	*Staphylococcus aureus* (including methicillin-resistant isolates)

		Enterococcus faecalis (vancomycin-susceptible isolates only) *Streptococcus agalactiae*

VI Standards/Guidance Documents Referenced:

- FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)
- CLSI M07-A11 "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Eleventh Edition" Vol. 38 No. 2 (January 2018)
- CLSI M100-M30, "Performance Standards for Antimicrobial Susceptibility Testing"; Thirtieth Edition (January 2020)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Reproducibility testing for the VITEK 2 AST-GP card with Fosfomycin was conducted at three clinical sites using a panel of ten *Enterococcus faecalis* isolates. 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 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 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.

All MIC values were on-scale and within one doubling dilution of the mode MIC. The testing resulted in overall reproducibility of 100% for each dilution method and VITEK 2 system, which is 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 *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213, were tested a sufficient number of times (i.e., at least 20/site) at each testing site using both the VITEK 2 card and agar dilution (AD) reference method. 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 are summarized in **Table 1** below.

Table 1. Quality Control Results for Fosfomycin: VITEK 2 (Auto-Dilution and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Organism	VITEK 2 Result Range[1]	FOS MIC (µg/mL)	VITEK 2 Auto-Dilution	AD	VITEK 2 Manual Dilution	AD	VITEK 2 Compact Manual Dilution	AD
Enterococcus faecalis ATCC 29212 Expected Result: 32 - 128 µg/mL		≤0.25						
		0.5						
		1						
		2						
		4						
	*	8		1				
	*	16		1				
	*	32	2	64	2	43	2	43
	*	64	195	131	148	107	148	107
	*	128						
	*	256						
		512						
		≥1024						
Staphylococcus aureus ATCC 29213 Expected Result: 0.5 - 4 µg/mL		≤0.25						
		0.5						
		1		18		9		9
		2		65		58		58
		4		107		78		78
	*	8	197	9	149	7	150	7
	*	16						
	*	32			1			
	*	64	2		2		2	
	*	128						
	*	256						
		512						
		≥1024						

FOS: fosfomycin; AD: agar dilution

*denotes the on-scale MIC result range of the AST-GP Fosfomycin test

[1]The lowest concentration of Fosfomycin on the VITEK 2 card is 8 µg/mL and therefore does not include the full CLSI/FDA-recommended dilution range for QC testing of *S. aureus* ATCC 29213. An in-range VITEK result will be ≤ the lowest dilution on the card (i.e., ≤ 8 µg/mL). Obtaining this value was considered an indicator that the quality control test results were acceptable.

The VITEK 2 AST-GP Fosfomycin reporting range (≤8 to ≥256 µg/mL) does not include the CLSI/FDA-recommended dilution range for QC testing of *S. aureus* ATCC 29213 (0.5 - 4 µg/mL). As such, VITEK result with ≤ the lowest dilution on the card (i.e., ≤ 8 µg/mL) was considered to be "in-range". This is addressed in the following footnote to the *S. aureus* QC result range within the Quality Control table in the device labeling:

> *Does not include the CLSI/FDA-recommended dilution range for QC testing with this organism.*

Acceptance of QC results for the VITEK 2 AST-GP Fosfomycin was based on the *Enterococcus faecalis* ATCC 29212 strain since they provided results confirming the range.
Both the auto-dilution and the manual dilution methods for VITEK 2 and the manual dilution for VITEK 2 Compact QC results were within the expected range >95% of the time, which is acceptable.

Two ancillary quality control organisms were tested throughout comparative testing by agar dilution reference method only. This was done to perform further quality control of the agar dilution plates. The organisms tested were *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. QC results for the agar dilution method were within the expected result range >95% of the time. *E. coli* ATCC 25922 was within range 98.1% (205/209) and *P. aeruginosa* ATCC 27853 was within range 97.6% (206/211).

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
A total of 399 clinical and challenge isolates were tested by VITEK 2 Fosfomycin. No growth failure was recorded and all 399 isolates have VITEK 2 AST results available.

6. Detection Limit:

   Not applicable

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
   Testing of fosfomycin on the VITEK 2 AST-Gram Positive card was performed at five clinical sites. There were 316 clinical isolates and 83 challenge isolates tested for a total of 399 isolates. Results obtained with the VITEK 2 AST-Gram Positive card with fosfomycin

were compared to results obtained with the CLSI recommended agar dilution testing conditions. The MIC result range for the VITEK 2 AST-Gram Positive Fosfomycin is ≤8 to ≥256 µg/mL for *Enterococcus faecalis*. The reference method testing consisted of two-fold serial dilutions of fosfomycin with a range of ≤8 to ≥256 µg/mL. The testing conditions for the reference method consisted of the following:

- Medium – Mueller Hinton agar with addition of 25 µg/mL of glucose-6-phosphate and appropriate dilutions of antimicrobial solution added
- Inoculum – Direct colony suspension
- Incubation – 35°C ± 2°C; 16-20 hours

The VITEK 2 AST cards were inoculated with test organisms using the auto-dilution method (VITEK 2) and 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 316 clinical isolates were evaluated at five sites: 25.9% were considered contemporary isolates (isolated from clinical specimen and tested within 6 months) and 74.1% were stock isolates. Complete test results are available for all 316 clinical isolates. All clinical isolates were tested with the auto-dilution option of the VITEK 2.

A total of 83 *E. faecalis* challenge isolates 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, a sufficient number of resistant isolates were not available for *E. faecalis*. 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.*
>
> *[fos02n] Fosfomcyin (fos02n): E. faecalis*

Clinical and Challenge Data –VITEK 2 Auto-Dilution
VITEK 2 AST-GP Fosfomycin performance was determined with 399 isolates (316 clinical isolates and 83 challenge isolates) and evaluated based on susceptibility testing interpretive criteria (breakpoints) established for *E. faecalis*:

Table 2. Performance of All Clinical and Challenge Isolates for Fosfomycin: VITEK 2 Auto-Dilution

Organism Type	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	#S	min	maj	vmj
***Enterococcus faecalis* [Breakpoints (µg/mL): ≤8 (S), 128 (I), ≥256 (R)]**													
Clinical	316	306	96.8	316	306	93.0	303	95.9	1	302	13	0	0
Challenge	83	82	98.8	83	82	98.8	83	100	0	83	0	0	0
Combined	**399**	**388**	**97.2**	**399**	**388**	**97.2**	**386**	**96.7**	**1**	**385**	**13**	**0**	**0**

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
min – minor errors
maj – major errors
vmj – very major errors
S – Susceptible isolates

The overall performance of *Enterococcus faecalis* is acceptable with an EA of 97.2% and a CA of 96.7%. There were no major or very major errors.

Challenge Data –VITEK 2 and VITEK 2 Compact Manual Dilution
The 83 challenge isolates were also tested at one site with the manual dilution option for the VITEK 2 and VITEK 2 Compact systems (**Table 3**).

Table 3: Performance of Challenge Isolates for Fosfomycin: VITEK 2 *Manual Dilution*

System	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	#S	min	maj	vmj
***Enterococcus faecalis* [Breakpoints (µg/mL): ≤8 (S), 128 (I), ≥256 (R)]**													
VITEK 2	83	82	98.8	83	82	98.8	83	100	0	83	0	0	0
VITEK 2 Compact	83	82	98.8	83	82	98.8	83	100	0	83	0	0	0

The overall performance of *Enterococcus faecalis* is acceptable with an EA of 98.8% and a CA of 100% with both the VITEK 2 and VITEK 2 Compact systems. There were no major or very major errors.

Resistance Mechanism Characterization
The FDA drug label for Fosfomycin does not indicate any specific mechanisms of resistance.

MIC Trends
A trending analysis was conducted using the combined data (clinical and challenge) obtained from the VITEK 2 auto-dilution method for *E. faecalis* (**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. 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 4. Trending by *E. faecalis* (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**
Enterococcus faecalis	399	18 (4.51)	138 (34.59)	243 (60.90)	56.39% (50.91 to 61.33)	Yes (High)

A trend toward higher MIC values was observed for *E. faecalis*. The following footnote to the performance table is included in the package insert to address the trending observed for VITEK 2 AST-Gram Positive Fosfomycin:

VITEK 2 AST-Gram Positive Fosfomycin MIC values tended to be in exact agreement or at least one doubling dilution higher when testing Enterococcus faecalis compared to the CLSI reference agar dilution method.

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):

   Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The FDA-recognized susceptibility interpretive criteria for Fosfomycin are listed in **Table 5.**

Table 5. FDA-Recognized Interpretive Criteria for Fosfomycin (µg/mL)[a]

Organism	Susceptible	Intermediate	Resistant
Enterococcus faecalis	≤64	128	≥256

[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-GP Fosfomycin when revised breakpoints for fosfomycin 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 fosfomycin 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.