510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K230864

B Applicant

BioMérieux, Inc

C Proprietary and Established Names

VITEK 2 AST-Gram Positive Daptomycin (≤0.12 - ≥8 µg/mL), VITEK 2 AST-GP Daptomycin (≤0.12 - ≥8 µg/mL), VITEK 2 AST-GP Daptomycin

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 update the VITEK 2 AST GP Daptomycin device labeling to include updated FDA-recognized breakpoints for *Enterococcus faecalis* as published in the FDA STIC website and add a claim for testing of vancomycin-resistant *E. faecalis* due to FDA-recognized breakpoints

Breakpoints for *Staphylococcus aureus* (also indicated for use with this device) remain unchanged.

Previously obtained QC and reproducibility data are applicable to this reevaluation.

B Measurand:

Daptomycin ≤0.12 - ≥8 µg/mL

C Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test for daptomycin

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 Daptomycin 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 Daptomycin is a quantitative test. Daptomycin 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 (vancomycin-susceptible isolates only)
Staphylococcus aureus (including methicillin-resistant isolates)

In vitro data are available. but their clinical significance is unknown:
Enterococcus faecalis (vancomycin-resistant isolates)

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.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):
Daptomycin (dap02n): *Enterococcus faecalis* when the VITEK 2 MIC is 4µg/mL due to the occurrence of minor errors resulting in a category agreement below 90%; *Streptococcus agalactiae*

The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing.
Daptomycin (dap02n): *Enterococcus faecalis*

D Special Instrument Requirements:
VITEK 2 and VITEK 2 Compact Systems using VITEK 2 Systems 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 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-GP Daptomycin has the following concentrations in the card: 0.5, 1, 2, 4, and 16 (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 AST-GP Daptomycin test is ≤0.12 - ≥8 µg/mL. For all species, the MIC result range indicates that the VITEK 2 system is capable of producing the following MIC results ≤0.12, 0.25, 0.5, 1, 2, 4, and ≥8 µg/mL for AST-GP Daptomycin test. This means the VITEK 2 systems does not provide results lower than 0.12 µg/mL, or greater than 8 µg/mL for the AST-GP Daptomycin 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 Gram Positive Daptomycin (≤0.12 - ≥8 µg/mL)

B Predicate 510(k) Number(s):
K091126

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device K230864	Predicate K091126
Device Trade Name	VITEK 2 AST-GP Daptomycin (≤0.12 - ≥8 µg/mL)	VITEK 2 AST-GP Daptomycin (≤0.12 - ≥8 µg/mL)
General Device Characteristic Similarities		
Intended Use/Indications For Use	VITEK 2 AST-GP Daptomycin 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-GP Daptomycin is a quantitative test. Daptomycin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial. 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 *Enterococcus* spp., *Staphylococcus* spp., and *Streptococcus agalactiae* to antimicrobial agents when used as instructed.	Same
Test Methodology	Automated quantitative antimicrobial susceptibility test	Same

Device & Predicate Device(s):	Device K230864	Predicate K091126
	for use with the VITEK 2 and VITEK 2 Compact Systems to determine the in vitro susceptibility of microorganisms	
Antimicrobial Agent	Daptomycin	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	Discriminant Analysis	Same
Type of Test	Quantitative	Same
Concentrations	0.5, 1, 2, 4, 16	Same
General Device Characteristic Differences		
Breakpoints	*Staphylococcus aureus:* (S/I/R) ≤ 1 / - / - *Enterococcus faecalis:* (S/I/R) ≤ 2 / 4 / ≥8	*Staphylococcus aureus*: (S/I/R) ≤ 1 / - / - *Enterococcus faecalis:* (S/I/R) ≤ 4 / - / -
Indicated Organisms	Active both *in vitro* and in clinical infections: *Enterococcus faecalis* (vancomycin- susceptible isolates only) *Staphylococcus aureus* (including methicillin-resistant isolates) *In vitro* data are available. but their clinical significance is unknown: *Enterococcus faecalis* (vancomycin- resistant isolates)	Active both *in vitro* and in clinical infections: *Enterococcus faecalis* (vancomycin- susceptible isolates only) *Staphylococcus aureus* (including methicillin-resistant isolates)

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-A5, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Fifth Edition", (January 2000)

3. CLSI M07, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Seventh Edition", Vol. 38 No. 2 (January 2006)
4. CLSI M100-ED33, "2023 Performance Standards for Antimicrobial Susceptibility Testing; 33rd Edition (March 2023)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing for the VITEK 2 Gram Positive Daptomycin was previously evaluated during review of K091126 and was determined to be 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, Inoculum and Growth failure for the VITEK 2 Gram Positive Daptomycin were performed in support of clearance of K091126 and were determined acceptable. QC testing specific to the changes in breakpoints was not performed in the current submission since the QC ranges used in K091123 were either unchanged (*E. faecalis* ATCC 29212) or narrowed (*S. aureus* ATCC 29213; range expanded from 0.25 – 1 µg/mL to 0.12 - 1 µg/mL) and therefore would not negatively impact QC performance. QC results with unchanged and expanded QC ranges are shown in **Table 1**.

In summary, the QC organisms recommended by both the FDA and CLSI, namely *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213, were tested using the reference broth microdilution (BMD) method as well as the VITEK 2 GP Daptomycin by the automatic and the manual dilution methods during the clinical study a minimum 20 times/site. QC results for the VITEK 2 Daptomycin were within the expected results range >95% of the time for both automatic and manual dilution modes of the VITEK 2, which is acceptable.

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

Organism	VITEK 2 Result Range	BMD Result Range (µg/mL)	VITEK 2 Auto-Dilution	BMD	VITEK 2 Manual Dilution	BMD
E. faecalis **ATCC 29212**		≤0.03				
		0.06				
	≤0.12	0.12				
	0.25	0.25				
Expected Result	0.5	0.5				
1 – 4 µg/mL	1	1				
	2	2		1		1
	4	4	99	90	98	89
	≥8	8		10		8
		≥16				
S. aureus **ATCC 29213**		≤0.03				
		0.06				
	≤0.12	0.12				
	0.25	0.25	51	73	52	73
Expected Result	0.5	0.5	36	25	36	25
0.12 – 1 µg/mL	1	1	1		10	
	2	2	1			
	4	4				
	≥8	8				
		≥16				

6. Detection Limit:

   Not applicable

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Performance after reanalysis

The VITEK 2 AST-GP Daptomycin (≤0.12 - ≥8 µg/mL) which was originally cleared in K091126, included indications for *Enterococcus faecalis (vancomycin-susceptible strains only)* and *Staphylococcus aureus (including methicillin-resistant strains)* tested with the VITEK 2 auto dilution and the VITEK 2 manual dilution and compared to the CLSI broth microdilution reference method.

The performance of the VITEK 2 AST-GP Daptomycin card with *Enterococcus faecalis* using revised interpretive criteria currently recognized by FDA for both vancomycin-susceptible and vancomycin-resistant isolates was evaluated in the current submission using data obtained in support of K091126.

Since there was no change in the design or the daptomycin dilution range of the VITEK 2 AST-ST card, the performance evaluation was achieved via re-analysis of the MIC data of the original 510(k) submission (K091126). For this review, the current daptomycin interpretive criteria are applied to *E. faecalis* according to the FDA STIC webpage.

A total of 270 (clinical and challenge) *E. faecalis* isolates were tested using the VITEK 2 with automatic dilution. The isolates included 240 clinical isolates and 30 challenge isolates. Although the 270 isolates were included in studies reported in the original daptomycin submission (K091126), the original decision summary evaluated a total of only 196 clinical and challenge *E. faecalis* isolates. This was because 44 vancomycin-resistant isolates of *E. faecalis* were excluded from the final analysis due to a lack of recognized breakpoints at that time. These isolates are included in the current analysis.

Results of the re-analyzed 270 *E. faecalis* clinical and challenge isolates tested by the auto-dilution method are summarized in **Table 2**. Original data obtained with *S. aureus* were not reanalyzed since the interpretive criteria remain unchanged since the original submission. The VITEK 2 system with the manual dilution method results of the reanalyzed challenge data with updated *E. faecalis* interpretive data are summarized in **Table 3**.

Table 2. Reanalysis of the Performance of *Enterococcus faecalis* and Original Performance Data for *Staphylococcus aureus* for the Auto Dilution VITEK 2 AST-GP Daptomycin.

	Total	#EA	%EA	Eval EA Total	Eval EA #	Eval EA %	#CA	%CA	#R or NS	#S	min	maj	vmj
***Enterococcus faecalis* ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	240	232	96.7	237	229	96.6	202	84.2	6	195	37	0	1
Challenge	30	30	100	29	29	100	26	86.7	2	24	4	0	0
Combined	270	262	97	266	258	97	228	84.4	8	219	41	0	1
***Staphylococcus aureus* ≤1 (S), ≥2 (NS)**													
Clinical	150	142	94.7	148	140	94.6	148	98.7	0	150	0	2	0
Challenge	44	41	93.2	41	38	92.7	44	100	9	35	0	0	0
Combined	194	183	94.3	189	178	94.2	192	99.0	9	185	0	2	0

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

Essential Agreement (EA) occurs when there is agreement between the MIC result of the reference method and that of the 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 or those in which an off scale result is at least two doubling dilutions from the on scale result. 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 combined Essential Agreement (EA) is >90% which is acceptable, as described in the "Class II Special Control Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 2009" (AST guidance).

The updated breakpoints for *E. faecalis* lowered the susceptible breakpoint by one two-fold dilution to ≤2 (S), and introduced breakpoints for intermediate (4) and resistant (≥8) categories. Applying the updated breakpoints for *E. faecalis* reduced the combined Category Agreement (CA) from 97.4% to 84.4%. This is due to the new intermediate category and increase in the number of test results (from 196 isolates analyzed for the predicate in K091126 to 270 isolates analyzed in the current submission). There were 41 minor errors (15.2%), one very major error (0.4%), and no major errors.

The AST Guidance indicates that a CA of <90% may be acceptable if the EA of evaluable results is very good and the majority of discrepancies are minor. Since a majority of the categorical errors were minor and the EA of evaluable results is >90%, the following limitation is added to the package insert to address the low CA, in addition to the previously determined unacceptable performance when testing *Streptococcus agalactiae*:

> *Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):*
> *Daptomycin (dap02n): Enterococcus faecalis when the VITEK 2 MIC is 4µg/mL due to the occurrence of minor errors resulting in a category agreement below 90%; Streptococcus agalactiae*

Table 3. Reanalysis of Performance of the Original *Enterococcus faecalis* Challenge Isolates with the VITEK 2 System (Manual Dilution)

	Total	#EA	%EA	Eval EA Total	Eval EA #	Eval EA %	#CA	%CA	#R	#S	min	maj	vmj
***Enterococcus faecalis* ≤2 (S), 4 (I), ≥8 (R)**													
Challenge	30	30	100	29	29	100	25	83.3	1	22	5	0	0

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

Essential Agreement (EA) occurs when there is agreement between the MIC result of the reference method and that of the 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 or those in which an off scale result is at least two doubling dilutions from the on scale result. 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 original submission, VITEK 2 AST-GP Daptomycin (K091126) did not include VITEK 2 Compact data. This was considered acceptable based on an equivalency study in K050002.

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included in the device labeling to address testing 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.

MIC Trending Analysis

A trending analysis was performed using the combined (challenge and clinical) data obtained in K091126 from the VITEK 2 auto-dilution method for all *E. faecalis* isolates.

This trending calculation takes into account the MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Evidence of trending is determined to occur when the difference between the percentage of isolates with higher vs. lower readings is > 30% and for which the confidence interval is determined to be statistically significant. If trending shows higher or lower MIC values compared to the reference, this must be addressed in the labeling.

No trending was observed with *E. faecalis*. For completeness, although not included in K091126, the trending analysis for *S. aureus* has been calculated and included in **Table 4**.

Table 4. Trending Analysis for *E. faecalis* and *S. aureus* (clinical and challenge isolates) with Daptomycin and the VITEK 2 Automated Dilution

Organism Inoculation Method	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
E. faecalis	266	44 (16.5)	153	69 (25.9)	9% (2%, 16%)	No
S. aureus	191	17 (8.9)	101	73 (38.22)	29% (21%, 37%)	No

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 daptomycin are listed in **Table 5**.

Table 5. FDA Recognized Interpretive Criteria for Daptomycin[a]

Pathogen	Minimum Inhibitory Concentrations (µg/mL)		
	S	I	R
E. faecalis (including vancomycin-resistant isolates)	≤2	4	≥8
S. aureus (including methicillin-resistant isolates)	≤1	-	-

S = Susceptible; I = Intermediate; R = Resistant
[a] According to FDA STIC Website

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device when evaluated with the current FDA-recognized daptomycin breakpoints

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 System with daptomycin when revised breakpoints for daptomycin 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 daptomycin 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.