

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

A. 510(k) Number:

k093076

B. Purpose for Submission:

To obtain a substantial equivalence determination for this premarket notification for the addition of Doxycycline to the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems.

C. Measurand:

Doxycycline concentrations of 0.25, 1, 2, and 4 µg/mL

D. Type of Test:

The minimum inhibitory concentration (MIC) is determined using qualitative growth based detection algorithm using predetermined growth threshold. The MIC reporting result range of the card is $\leq 4 - \geq 16$ µg/mL.

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

VITEK[®] 2 Gram Positive Doxycycline

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645	Microbiology -83

H. Intended Use:

1. Intended use(s):

The VITEK[®] 2 AST is intended to be used with the VITEK[®] 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for most clinically significant aerobic gram-negative bacilli, *Staphylococcus spp.*,

Enterococcus spp., *Streptococcus agalactiae*, and *S. pneumoniae*.

The VITEK[®] 2 Gram Positive Susceptibility Card 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 of *Staphylococcus spp.*, *Enterococcus spp.*, and *Streptococcus agalactiae* to antimicrobial agents when used as instructed in the Online Product Information.

2. Indication(s) for use:

VITEK[®] 2 Gram Positive Doxycycline 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 Gram Positive Doxycycline is a qualitative test. Doxycycline has been shown to be active against the microorganisms listed below according to the FDA label for the antimicrobial.

Active *in vitro* and in clinical infections:

Staphylococcus aureus

The VITEK[®] 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK[®] 2 and VITEK[®] 2 Compact 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 agalactiae*, and *S. pneumoniae*.

3. Special conditions for use statement(s):

Prescription use only.

4. Special instrument requirements:

For use with the VITEK 2 and VITEK 2 Compact Systems

I. Device Description:

VITEK 2 AST card containing the test is inoculated with a standardized suspension of the organism to be tested. The VITEK 2 System automatically fills, seals, and places the card into the incubator/reader while the VITEK 2 Compact System has manual filling, sealing and loading operation. The incubated card is optically monitored by the VITEK 2 Systems for growth within each well in the card throughout the incubation cycle. At the completion of incubation, results are automatically calculated once a predetermined growth threshold is reached. A report is then generated that

contains the MIC value and the interpretive category result (S.I.R) for each antibiotic contained on the card.

The MIC ranges, interpretive criteria and equivalent concentrations are as follows:

VITEK 2 AST-GP	Equivalent Standard Method Concentration by Efficacy in µg/mL	MIC Ranges and FDA/CLSI Categories MIC* in µg/mL:		
		S	I	R
Doxycycline	0.25, 1, 2, 4	≤ 4	8	> 16

S = Susceptible: Attainable levels in blood or tissue on usual usage, including oral administration when applicable.

I = Intermediate: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated (e.g. quinolones and B-lactams in urine), or when a higher than normal dosage of drug can be used (e.g. B-lactams). The “intermediate” category also includes a “buffer zone” which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

R = Resistant to usually achievable systemic concentrations.

J. Substantial Equivalence Information:

1. Predicate device name(s):

VITEK 2 Gram positive Daptomycin

2. Predicate K number(s):

k091126

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Determining quantitative and qualitative susceptibility to antimicrobial agents	Same
Inoculation and test organism	Isolated colonies of <i>Staphylococcus aureus</i>	Same
Instrument	Test are run on both the VITEK 2 and VITEK 2 Compact Systems	Same

Similarities		
Item	Device	Predicate
Test Card	The VITEK 2 card, including base broth	Same

Differences		
Item	Device	Predicate
Antibiotic	Doxycycline-specific concentrations	Daptomycin-specific concentrations
Reading algorithm	Unique to Doxycycline	Unique to Daptomycin

K. Standard/Guidance Document Referenced (if applicable):

“Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071462.pdf>

Clinical Laboratory Standards Institute (CLSI) Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard -7th Edition, Document M7-A8.

CLSI Performance Standards for Antimicrobial Susceptibility Testing – 18th Informational Supplement, M100-S19.

L. Test Principle:

Automated growth based detection using attenuation of light measured by an optical scanner. The optics used in the systems use visible light to directly measure organism growth. Transmittance optics are based on an initial light reading of a well before significant growth has begun. Periodic light transmittance samplings of the same well measure organism growth by how much light is prevented from going through the well. The VITEK 2 System monitors the growth of each well in the card over a defined period of time. An interpretive call is made between 4 and 16 hours for a “rapid” read but may be extended to 18 hours in some instances. 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 on the card. The VITEK 2 Gram Positive Doxycycline will have the following concentrations: 0.25, 1, 2, and 4 µg/mL. The VITEK 2 Gram Positive Doxycycline provides MIC results ranging from ≤4 - ≥16 µg/mL.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility was conducted at three study sites. Ten Gram positive isolates were tested at each site and testing was performed in triplicate over three days with the VITEK 2 AST Gram positive Doxycycline. The testing was performed using both the manual dilution method and the automated dilution mode. Testing was conducted on the VITEK 2 instrument.

For the sake of reproducibility calculations, off-scale values are handled in two ways; “best case” and “worst case” scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value.

The overall reproducibility was >95% with +/- one dilution observation. For Automatic Dilution, the VITEK 2 AST Gram positive Doxycycline gave overall reproducibility values of 100% and 98.9% based on best case and worst case calculations, respectively. Identical overall results were obtained by Manual Dilution.

A similar reproducibility study was conducted by testing on the VITEK 2 Compact instrument. The VITEK 2 AST Gram positive Doxycycline card gave a best case and worst case between site reproducibility of 100% by Manual Dilution. Only Manual Dilution testing was conducted since the VITEK 2 Compact system does not have a functionality to support automatic dilution to inoculate the card.

b. *Linearity/assay reportable range:*

Not applicable

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

The recommended QC isolates were tested on every test occasion with the reference method and the VITEK 2 System. The reference method QC results were in range for every day that they were tested. The VITEK 2 was tested a sufficient number of times to demonstrate that the system can produce QC results in the recommended range.

Quality Control was performed during the studies using both the auto-dilution and the manual method of diluting the organisms on the VITEK 2 System. Results demonstrated that methods were comparable with the same mode.

Quality Control Results with the VITEK 2 System

Organism	Concentration (µg/mL)	Reference	VITEK 2 GP Doxycycline	
			Auto Dilution	Manual Dilution
<i>E. faecalis</i> ATCC 29212 Acceptable MIC range: 2-8 µg/mL	≤0.015			
	0.03			
	0.06			
	0.12			
	0.25			
	0.5*			
	1*			
	2*	46		2
	4*	76	69	47
	8*		53	72
	16*			
	≥32			
	<i>S. aureus</i> ATCC 29213 Acceptable MIC range: 0.12-0.5 µg/mL	≤0.015		
0.03				
0.06				
0.12		31		
0.25		87		
0.5*		3	121	120
1*				
2*				
4*				
8*				
16*				
≥32				

* VITEK Card Result Range

At least one Quality control organism was in control for the reference on all days. Quality Control results for the VITEK 2 System using either inoculation dilution method demonstrated that the VITEK 2 System could produce the expected quality control results.

A similar QC study was conducted to evaluate the VITEK 2 Compact System. Results were compared to the expected CLSI QC results. All results for the Vitek 2 Compact System were within the expected QC ranges 100% of the time. However, all values for The VITEK 2 were at 0.5 µg/mL, the top of the QC range.

Quality Control Results with the VITEK 2 Compact System

Organism	Concentration (µg/mL)	Reference	VITEK 2 GP Doxycycline	
			Manual Dilution	
<i>E. faecalis</i> ATCC 29212 Acceptable MIC range: 2-8 µg/mL	≤0.015			
	0.03			
	0.06			
	0.12			
	0.25			
	0.5*			
	1*			
	2*		1	
	4*	60	35	
	8*		24	
	16*			
	≥32			
	<i>S. aureus</i> ATCC 29213 Acceptable MIC range: 0.12-0.5 µg/mL	≤0.015		
0.03				
0.06				
0.12		20		
0.25		18		
0.5*		22	60	
1*				
2*				
4*				
8*				
16*				
≥32				

* VITEK Card Result Range

Inoculum density control was monitored using the DensiChek2 instrument. This was standardized weekly with all results recorded and in the expected range.

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:*

Performance was established through an initial clinical study which was conducted initially at four sites (three external and one internal). In addition, another clinical study was conducted at one external site to include additional fresh isolates of *S. aureus*.

Testing was done using the VITEK 2 Gram positive cards with Doxycycline and the broth microdilution method using Mueller Hinton (MH) broth (cation adjusted) supplemented with 50 µg/mL calcium. The MH broth was incubated at 35°C in ambient air for up to 18 hours. The inoculum was prepared with direct colony suspension. The testing included both fresh clinical isolates and stock isolates along with a challenge set with known results. Two methods of inoculation (manual and auto dilution) were evaluated. Clinical testing was performed using the automated method of inoculation and the challenge set was tested using both the manual and the auto dilution method. A comparison was provided to the reference method with the following agreement.

AutoDilution

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Staphylococcus aureus</i>												
CLINICAL	300	299	99.7	13	12	92.3	297	99	2	0	0	3
CHALLENGE	86	84	97.7	70	68	97.1	76	88.4	14	0	0	10
COMBINED (CLINICAL AND CHALLENGE)	386	383	99.2	83	80	96.4	373	96.6	16	0	0	13

EA-Essential Agreement

CA-Category Agreement

NS-not susceptible

Essential agreement (EA) is when the VITEK 2 panels agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the VITEK 2 panel result interpretation agrees exactly with the reference panel result interpretation. Evaluable EA is when the MIC result is on scale for both the VITEK 2 and the reference and have on-scale EA.

A CA of 88.4% observed for challenge isolates is slightly lower than the 90% recommended in the FDA guidance. However, this is acceptable since a high

EA was observed for the test and all discrepancies were minor errors (i.e. no very major or major errors). Also, another study on the VITEK 2 Compact Systems demonstrated acceptable EA and CA (See below).

The challenge set of organisms was also tested at one site using the manual method of inoculation with the following performance demonstrating that similar results are seen with both inoculation methods.

Manual Dilution

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Staphylococcus aureus</i> CHALLENGE	86	85	98.8	69	68	98.6	76	88.4	14	0	0	10

A total of 86 Challenge isolates of *S. aureus* were also tested in the VITEK 2 Compact using the manual dilution method. A comparison was provided to the reference method with the following agreement.

Manual Dilution

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Staphylococcus aureus</i> CHALLENGE	86	83	96.5	68	66	97.1	78	90.7	14	0	1	7

b. *Matrix comparison:*

Not Applicable

3. Clinical Studies:

a. *Clinical Sensitivity:*

Not Applicable

b. *Clinical specificity:*

Not Applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

Not Applicable

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR section 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.