

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

A. 510(k) Number:

K072695

B. Purpose for Submission:

The addition of the antibiotic Tigecycline to the VITEK®2 Antimicrobial Susceptibility Test (AST) System.

C. Measurand

VITEK ® 2 Gram Positive Tigecycline (≤ 0.12 - ≥ 2 µg/ml)

D. Type of Test:

Quantitative growth based detection algorithm using optics light detection

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

Vitek®2 Gram Positive Tigecycline.

G. Regulatory Information:

1. Regulation section:
866.1645 Short-Term Antimicrobial Susceptibility Test System
2. Classification:
II
3. Product Code:
LON System, Test, Automated, Antimicrobial Susceptibility, Short Incubation
4. Panel:
83 Microbiology

H. Intended Use:

1. Intended use(s):
VITEK® 2 Gram Positive Susceptibility Card is intended for use with VITEK® 2 System in clinical laboratories as an *in vitro* test to determine the susceptibility of gram positive organisms to Tigecycline when used as instructed in the System Product Information manual.

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*.

2. Indication(s) for use:

This submission is for the addition of the antibiotic tigecycline at concentrations of 0.25, 0.5, and 1.0 µg/ml to VITEK® 2 Gram Positive (AST-GP) panels. It 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 Tigecycline has been shown to be active *in vitro* against *Enterococcus faecalis* (vancomycin-susceptible), *Staphylococcus aureus* (methicillin – susceptible and –resistant isolates), and *Streptococcus agalactiae*; and against *Enterococcus faecium* (vancomycin-susceptible and - resistant isolates), *Staphylococcus epidermidis*, *Staphylococcus haemolyticus* and *Enterococcus casseliflavus*, but the clinical significance is unknown.

3. Special condition for use statement(s):

- a. The VITEK 2 AST cards cannot be used with direct clinical specimens or other sources containing mixed flora. Any change or modification in the procedure may affect the results.
- b. The ability of Tigecycline to detect resistance with *Enterococcus faecalis* (vancomycin-susceptible), *Staphylococcus aureus* (methicillin – susceptible and – resistant isolates), and *Streptococcus agalactiae* is unknown because these strains have not yet been detected and should be retested. If a “non-susceptible” result is obtained the strain should be submitted to reference laboratory for further testing.
- c. Prescription Use Only

4. Special instrument Requirements:

Not Applicable

I. Device Description:

Each VITEK® 2 test card contains 64 microwells. A control well, that contains only microbiological culture medium is resident on all cards, with the remaining wells containing pre-measured amounts of a specific antibiotic combined with culture medium. A suspension of organism is made in 0.45-0.5% sterile saline from a pure culture in a clear plastic polystyrene tube and standardized to a McFarland 0.5 standard using the DensiChek Turbidity meter. The desired card (s) are placed in the cassette along with an empty tube for the preparation of a bacterial suspension. The cassette is placed into the VITEK® 2 instrument where a susceptibility test will be automatically diluted from the ID suspension by the Vitek® 2. Alternately, a manual dilution specific for each AST product type card can be made. The cards are then automatically vacuum filled; the tubes are cut and the cards sealed prior to proceeding to the Incubator Loading Station. Cards are then transferred from the cassette into the carousel for incubation (35.5° C) and optical scanning during testing. Readings are performed every 15 minutes.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Vitek 2 Gram Positive Daptomycin
2. Predicate K number(s):
K050075

3. Comparison with predicate

Similarities		
Item	Device	Predicate
Test Card	VITEK® 2 card format with base broth	same
Instrument	VITEK® 2 and VITEK ®2 Compact System	same
Dilution methods	Auto-dilution and manual	same
Differences		
Item	Device	Predicate
Antibiotic	Tigecycline	Daptomycin
Test organisms	<i>Enterococcus faecalis</i> (vancomycin-susceptible), <i>Staphylococcus aureus</i> (methicillin – susceptible and –resistant isolates), and <i>Streptococcus agalactiae</i>	<i>Enterococcus faecalis</i> <i>Staphylococcus aureus</i> <i>Streptococcus agalactiae</i> <i>Enterococcus faecium</i> <i>Staphylococcus epidermidis</i> and <i>Staphylococcus haemolyticus</i>
Reading algorithm	Unique for Tigecycline	Unique for Daptomycin

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

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”; CLSI M7 (M100-S16) “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard”; CLSI Document M7-A7, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – Seventh Edition.

L. Test Principle:

Optics systems use visible light to directly measure organism growth. These 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. An interpretive call is made between 4 and 16 hours with the majority of the S.

pneumoniae between 5 and nine hours. The VITEK Susceptibility Card test is based on the microdilution minimum inhibitory concentration (MIC) technique with concentrations equivalent to standard method concentrations. Several parameters based on the growth characteristics observed are used to provide appropriate input for the MIC calculations. Discriminate analysis is used to develop the algorithm that determines the susceptibility result for all antimicrobials on the VITEK 2 system. The MIC result must be linked to an organism identification in order to determine a category interpretation. A category interpretation will be reported along with a MIC.

M. Performance Characteristics (if/when applicable):

An external evaluation was conducted with fresh and stock clinical isolates and challenge strains. The external evaluations were designed to confirm the acceptability of VITEK® 2 Gram Positive Tigecycline, using both the auto-dilution and the manual dilution methods, by comparing its performance with the CLSI broth microdilution reference method read at 24 hours.

This submission is for the AST Panel only. The ID System was not reviewed.

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility was demonstrated using a panel of 10 *Staphylococcus aureus* isolates in triplicate, each for three days at three sites with VITEK® 2 AST-GP13 Tigecycline, for a total of 270 results. The reproducibility did not include *Enterococcus spp.* isolates. There were a total of 12 off-scale results in the auto-dilution and in the manual dilution methods, respectively. The mode for the off-scale results was more susceptible than the on-scale results mode by greater than two dilutions. On-scale results were > 95 % reproducible for both dilutions methods.

b. *Linearity/assay reportable range:*

Not Applicable

c. *Traceability (controls, calibrators, or method):*

The recommended QC isolates were tested by VITEK 2 GP13 containing Tigecycline, and broth microdilution plates containing Tigecycline. QC organisms *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were tested at each clinical trial site. One *Streptococcus pneumoniae* ATCC 49619 quality control organism was tested throughout comparative testing with *Streptococcus agalactiae* by the reference method only (data not presented). This was done to perform further quality control of the broth microdilution panels supplemented with lysed horse blood. The VITEK 2 GP13 card was tested a sufficient number of times to demonstrate that the system can produce QC results in the recommended range > 95% of the time. The following tables provide the frequency of the results in each

concentration at each of the 3 testing sites for the manual and the auto-dilution (automated) dilution methods.

AUTO-DILUTION QC (Tigecycline– TGC)

QC ORGANISM	Concentration	Vitek 2	Reference
<i>Enterococcus faecalis</i> ATCC 29212 Expected Range 0.03-0.125 µg/mL	≤ 0.015625		
	0.03125		1
	0.0625		71
	0.0125 *	73	2
	0.25*	1	
	0.5 *		
	1 *		
	2 *		
	≥4		

* VITEK 2 Card Result Range

MANUAL-DILUTION QC (Tigecycline– TGC)

QC ORGANISM	Concentration	Vitek 2	Reference
<i>Enterococcus faecalis</i> ATCC 29212 Expected Range 0.03-0.125 µg/mL	≤ 0.015625		
	0.03125		1
	0.0625		70
	0.0125 *	71	2
	0.25*	2	
	0.5 *		
	1 *		
	2 *		
	≥4		

* VITEK 2 Card Result Range

AUTO-DILUTION QC (Tigecycline– TGC)

QC ORGANISM	Concentration	Vitek 2	Reference
<i>Staphylococcus aureus</i> ATCC 29213 Expected Range 0.03-0.25 µg/mL	≤ 0.015625		
	0.03125		
	0.0625		3
	0.0125 *	89	88
	0.25*		
	0.5 *	2	
	1 *		
	2 *		
	≥4		

* VITEK 2 Card Result Range

MANUAL -DILUTION QC (Tigecycline– TGC)

QC ORGANISM	Concentration	Vitek 2	Reference
<i>Staphylococcus aureus</i> ATCC 29213 Expected Range 0.03-0.25 µg/mL	≤ 0.015625		
	0.03125		
	0.0625		3
	0.0125 *	88	87
	0.25*		
	0.5 *	2	
	1 *		
	2 *		
	≥4		

* VITEK 2 Card Result Range

E. faecalis ATCC 29212 QC performance: The modes for the VITEK 2 GP13 results were one dilution more resistant than the modes of the reference methods for both dilution methods. Two results, in the VITEK2-GP13 (TGC), (2/73, 2.7%), were interpreted outside the expected QC result range of 0.03-0.12 µg/mL. However, overall QC results were within the expected range ≥95% of the time for both dilution methods, which is acceptable.

S. aureus ATCC 29213 QC performance: The modes for the VITEK 2-GP13 results were the same as the reference methods for both dilution methods. Two results, in the Vitek GP13 (TGC), (2/90, 2.2%), were interpreted outside the expected QC result range of 0.03-0.25 µg/mL. However, overall QC results were within the expected range ≥95% of the time for both dilution methods, which is acceptable.

No QC trending was observed.

Inoculum density control: A turbidity meter was used (DensiCheck) for the turbidity inoculation method. DensiChek Calibration verification procedure was also included.

- a. *Detection limit:*
Not Applicable
- b. *Analytical specificity:*
Not Applicable
- c. *Assay cut-off:*
Not Applicable

2. Comparison studies:

- a. *Method comparison with predicate device:*
Clinical testing was conducted at 3 sites. The addition of the antibiotic Tigecycline to the VITEK®2 Antimicrobial Susceptibility Test (AST) System included 862 clinical isolates of which 280 were fresh, along with a challenge set with known

results. Two methods of inoculation (manual and automated) were evaluated by both VITEK 2 AST-GP13 Tigecycline and broth microdilution dilution containing Tigecycline. All isolates with the exception of one completed incubation in the VITEK 2 AST-GP13 card in <16 hours. A panel of 105 organisms were used for Challenge testing at one site. Each challenge organism was tested one time by manual dilution, automatic dilution, and broth microdilution, and the Disk Approximation Test (data not presented). A comparison was provided to the reference method with the following agreement.

Clinical and Challenge Data - Automated Dilution Method comparison for Tigecycline (TGC)

	Total	EA	%EA	Total evaluable	EA of evaluable	%EA	CA	%CA	#R	min	maj	vmj
Clinical	858	N/A	N/A	N/A	N/A	N/A	853	99.4	3	0	3	2
Challenge	105	N/A	N/A	N/A	N/A	N/A	104	99.0	0	0	1	0
Combined	963	N/A	N/A	N/A	N/A	N/A	957	99.4	3	0	4	2

EA-Essential Agreement

maj-major discrepancies

CA-Category Agreement

vmj-very major discrepancies

R-resistant isolates

min- minor discrepancies

N/A – Not applicable (due to Categorical Agreement claim only)

Challenge Data - Manual Read Method comparison for Tigecycline (TGC)

	Total	EA	%EA	Total evaluable	EA of evaluable	%EA	CA	%CA	#R	min	maj	vmj
Challenge	105	N/A	N/A	N/A	N/A	N/A	105	100.0	0	0	0	0

The performance characteristics of the antimicrobial agents included in VITEK 2 GP13 cards were established using the manual and automated modes at multiple clinical laboratories. The VITEK 2 AST GP 13 card results were compared to results from a reference method prepared according to CLSI. Essential Agreement (EA) was calculated for clinical trial data. However, the VITEK 2 AST-GP13 Tigecycline claims are for Category Agreement (CA) only. A statement to that effect is included on the VITEK 2 AST-GP13 Tigecycline package insert. Category Agreement (CA), in this case, occurs when the VITEK 2 GP13 and the reference interpretative result agree as Susceptible or Non-susceptible.

The Clinical testing and Challenge testing using the automated method in the categorical agreement data demonstrated 2 very major discrepancies (vmj) and 3 major discrepancies (maj). There was only 1 major discrepancy (maj) in the Challenge set using the automated dilution method and no discrepancies produced using the manual dilution method as shown in the tables above. Additional data was provided focusing on the Vancomycin resistant *Enterococcus* spp., since their performance in Tigecycline, has

shown to be active *in vitro*, but their clinical significance is unknown. 37 Vancomycin Resistant Enterococcus (VREs) isolates showed no discrepancies in both clinical and challenge studies. Overall results demonstrated a combined CA of 99.4% which was very good.

The test device had a growth rate of >95%.

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)

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range

NAME OF THE ORGANISM	INTERPRETATIVE CRITERIA		
	Susceptible	Intermediate	Resistant
<i>Streptococcus</i> spp. (other than <i>S. pneumoniae</i> .)	≤ 0.25	* Not applicable	* Not applicable
<i>Enterococcus faecalis</i> (Vancomycin-susceptible isolates only)	≤ 0.25	* Not applicable	* Not applicable
<i>Staphylococcus aureus</i>	≤ 0.5	* Not applicable	* Not applicable
* The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of "Nonsusceptible" category should be submitted to reference laboratory for further testing.			

N. Proposed Labeling:

The expected value range, interpretive criteria and QC for Tigecycline (TGC) are the same as recommended by FDA. Additionally, the most current *in vivo* and *in vitro* organisms shown to be active with Tigecycline are also included in the package insert along with their appropriate interpretative limitations.

* The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of "Nonsusceptible" category should be submitted to reference laboratory for further testing.

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

O. Conclusion:

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