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

A. 510(k) Number:

K163006

B. Purpose for Submission:

To obtain a substantial equivalence determination for Tigecycline for testing of Gram negative bacilli on the VITEK®2 and VITEK®2 Compact Antimicrobial Susceptibility Test (AST) Systems.

C. Measurand:

The VITEK 2 AST-Gram Negative card contains the following concentrations of Tigecycline: 1.5, 4 and 8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result reporting range for the card is ≤0.5 - ≥8 µg/mL.

D. Type of Test:

Automated quantitative antimicrobial susceptibility for Tigecycline.

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK® 2 AST- GN Tigecycline (≤0.5 - ≥8 µg/mL)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1645 Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System

2. Classification:

   Class II

3. Product code:

LON - Fully automated short-term incubation cycle antimicrobial susceptibility system.

LTW – Susceptibility Test Cards, Antimicrobial

LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   83 Microbiology

H. Intended Use:

1. Intended use(s):

   The VITEK®2 Antimicrobial Susceptibility Tests (AST) are intended to be used with the VITEK®2 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* spp., and clinically significant yeast.

2. Indication(s) for use:

   VITEK® 2 AST-Gram Negative Tigecycline 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 Tigecycline is a quantitative test. Tigecycline 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

   Citrobacter freundii
   Enterobacter cloacae
   Escherichia coli
   Klebsiella oxytoca
   Klebsiella pneumonia

   In vitro data available but clinical significance is unknown

   Citrobacter koseri
   Enterobacter aerogenes
   Serratia marcescens

   The VITEK®2 Antimicrobial Susceptibility Tests (AST) are intended to be used with the VITEK®2 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* spp., and clinically significant yeast.

3. Special conditions for use statement(s):

   Prescription use only

   Limitation:

   "The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were not available at the time of comparative testing:

   Tigecycline: Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Serratia marcescens."

4. Special instrument requirements:

   VITEK® 2 and VITEK® 2 Compact Systems

I. 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 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 (up to 24 hours for *Streptococcus* Species). 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 anti-microbial 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 Tigecycline has the following concentrations in the card: 1.5, 4 and 8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK® 2 is ≤ 0.5 - ≥ 8 µg/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITEK® 2 AST-GN Cefepime

2. Predicate 510(k) number(s):

   K161227

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	Device	Predicate
Intended Use	VITEK® 2 AST-Gram Negative Tigecycline 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 Tigecycline is a quantitative test. Tigecycline 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: *Citrobacter freundii* *Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumonia* In vitro data available but clinical significance is unknown: *Citrobacter koseri*	VITEK® 2 Gram Negative Cefepime 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 Gram Negative Cefepime is a quantitative test. Cefepime 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: *Enterobacter* spp. *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* In vitro data available but clinical significance is unknown: *Citrobacter koseri* *Citrobacter freundii* *Pantoea agglomerans* *Klebsiella oxytoca*

	Enterobacter aerogenes *Serratia marcescens* The VITEK® 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK® 2 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 spp.* and clinically significant yeast.	*Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Serratia marcescens* The VITEK® 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK® 2 Systems for the automated quantitative or quantitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus spp., Enterococcus spp., Streptococcus spp.* and clinically significant yeast.
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 Gram negative bacilli	Same
Test Card	VITEK® 2 Gram Negative Susceptibility Test Card	Same
Instrument	VITEK® 2 and VITEK® 2 Compact Systems	Same

Differences		
Item	Device	Predicate
Antimicrobial	Concentration of antimicrobial in the test wells of the VITEK® 2 AST card and the analysis algorithms are unique for each antimicrobial. Tigecycline	Concentration of antimicrobial in the test wells of the VITEK® 2 AST card and the analysis algorithms are unique for each antimicrobial. Cefepime
Antimicrobial concentrations	1.5, 4, 8	0.25, 1, 4, 16, 32
Reporting Range	≤ 0.5 - ≥ 8	≤0.12 - ≥32
Analysis algorithm	Unique to Tigecycline	Unique to Cefepime

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

CLSI M100-S024: Performance Standards for Antimicrobial Susceptibility Testing
CLSI M07-A9: Methods for Dilution Antimicrobial Susceptibility Test (AST) Systems Aerobically
Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems

L. Test Principle:

The VITEK® 2 and VITEK® 2 Compact Systems utilize 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was conducted at three sites using ten isolates of gram-negative bacilli that were consistent with the intended use. Isolates were tested in triplicate over three days for a total of 270 data points. The isolates tested in the reproducibility study included *Enterobacter cloacae* (two isolates), *Enterobacter aerogenes* (two isolates), *Serratia marcescens* (three isolates), and *Klebsiella pneumoniae* (three isolates). Inocula were prepared both manually and using automatic dilution for testing in the VITEK2. Inocula were prepared manually for testing in the VITEK2 Compact. The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within +/- 1 dilution of the mode MIC value.

Using VITEK2 and automatic dilution, best case reproducibility was 99.6%; worst case reproducibility was 99.3%.

Using VITEK2 and manual dilution, all results were on scale and the reproducibility was 100%.

Using VITEK® 2 Compact and manual dilution, best case reproducibility was 99.6%; worst case reproducibility was 97.8%.

The reproducibility results were acceptable.

b. *Linearity/assay reportable range:*

N/A

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

Inoculum Density Check. The inoculum density was monitored using the DensiCHEK Plus™ instrument. The DensiCHEK Plus™ was standardized weekly with all results recorded and in expected range.

Purity Check: A purity check of all organisms was performed at the time of VITEK2 card inoculation. Only results obtained with pure cultures were evaluated.

Growth Failure Rate: During the course of the study there were no growth failures in the VITEK 2 AST-Gram Negative cards.

Quality Control Testing. The CLSI-recommended QC organism (*E. coli* ATCC 25922) was tested using both the VITEK 2 card and the reference method at each site using both the automatic dilution and manual dilution methods for the VITEK 2 and using the manual dilution method for the VITEK 2 Compact.

The expected range for *E. coli* ATCC 25922 with tigecycline is 0.03 – 0.25 µg/mL. The tigecycline concentrations included in the VITEK 2 AST-Gram Negative card are 1.5, 4, and 8 µg/mL and the reporting range is ≤0.5 - ≥8 µg/mL. Therefore, all results for the QC strain were off-scale for the VITEK 2 and VITEK 2 Compact Systems and were reported as ≤0.5 µg/mL (Table 2). In response to an FDA request for additional information regarding production and process controls to verify the performance of the device, the sponsor indicated that no other QC strains suitable for the *Enterobacteriaceae* claim could be identified that would cover the expected tigecycline MIC ranges based on CLSI or FDA drug label. Therefore, there was no specific recommendation for any additional QC strains to be tested, but the sponsor's internal QC process assures that the devices are produced and manufactured appropriateley. Furthermore, and to inform the end-user of this point, the sponsor included the following footnote to the QC table in the device labeling:

> *"The VITEK 2 Gram Negative tigecycline does not include the full CLSI/FDA-recommended dilution ranges for QC testing with this organism."*

Table 2. Quality Control Results for VITEK 2 with Automatic and Manual Dilution Inoculation Methods and for VITEK 2 Compact with the Manual Dilution Inoculation Method.

		VITEK 2 Automatic Dilution		VITEK 2 Manual Dilution		VITEK 2 Compact Manual Dilution	
Organism	Conc. (µg/mL)	Test	Ref.	Test	Ref.	Test	Ref.
E. coli ATCC 25922 Expected Range: 0.03 – 0.25 µg/mL	≤0.0156						
	0.03125						
	0.0625		110		56		56
	0.125		112		55		55
	0.25		2		1		1
	(≤)0.5*	225		112		112	
	1						
	2		1				
	4						
	8						
	≥16						

*The lowest dilution of the VITEK 2 MIC range is 0.5 µg/mL. Obtaining this value was considered as an indicator that the quality control test results were acceptable.

The quality control results were acceptable.

d. Detection limit:

N/A

e. Analytical specificity:

N/A

f. Assay cut-off:

N/A

2. Comparison studies:

a. Method comparison with predicate device:

Results obtained with the bioMerieux VITEK AST – Gram Negative card with tigecycline were compared to result obtained with the CLSI broth microdilution reference panel. The VITEK 2 AST-Gram Negative card with tigecycline contains the following concentrations of tigecycline: 1.5, 4 and 8 µg/mL (equivalent standard

method concentration by efficacy in µg/mL) and the reporting range is ≤0.5 - ≥8 µg/mL. The reference panel contained two-fold serial dilutions with a range of 0.0156 to 32 µg/mL.

Test inocula were standardized using the DensiCHEK Plus instrument. VITEK 2 AST – Gram Negative cards were inoculated using automatic dilution (for reading on the VITEK 2 instrument) or using a manual dilution method (for reading on the VITEK 2 instrument or on the VITEK 2 COMPACT instrument). Reference panels were inoculated as outlined in the CLSI document M07-A9.

A total of 637 *Enterobacteriaceae* clinical isolates were evaluated at three sites with VITEK 2 AST – Gram Negative cards inoculated by automatic dilution and interpreted using the VITEK 2 instrument. The majority of isolates were fresh (569 isolates, 89%); 68 isolates (11%) were stock isolates.

A total of 75 challenge isolates were tested at one site. The challenge set was tested with both card inoculation options (automatic dilution and manual dilution) on the VITEK 2 system and with the manual dilution on the VITEK 2 Compact system.

For MICs interpreted using the VITEK 2 system an inoculated using the automatic dilution method, the combined results from the clinical and challenge testing demonstrated a combined EA of 98.9% and CA of 98.6% (Table 3). A total of 96 isolates were determined to have evaluable results; the EA of the evaluable results was 91.7%. There were 2 major errors (0.3%) and no very major errors identified. The performance based on combined clinical and challenge data was acceptable.

Table 3: Performance of Clinical and Challenge Isolates, VITEK 2 Automatic Dilution Method

	Tot	No. EA	EA%	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Clinical	**637**	**629**	**98.7**	**78**	**70**	**89.7**	**630**	**98.9**	**1**	**636**	**5**	**2**	**0**
Challenge	**75**	**75**	**100**	**18**	**18**	**100**	**72**	**96.0**	**1**	**71**	**3**	**0**	**0**
Combined	**712**	**704**	**98.9**	**96**	**88**	**91.7**	**702**	**98.6**	**2**	**707**	**8**	**2**	**0**

EA – Essential Agreement (+/- 2 dilutions) **min –** minor discrepancies
CA – Category Agreement **maj** – major discrepancies
EVAL – Evaluable isolates **vmj** – very major discrepancies
R or NS – Resistant or non-susceptible isolates

Essential agreement (EA) occurs when there is agreement between the results of the reference method and that of VITEK2 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 VITEK2 test card and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the VITEK2 test card.

Challenge isolates interpreted using the VITEK2 and inoculated using the manual dilution method demonstrated an EA of 98.7% and a CA of 94.7% (Table 4). A total of 17 isolates were determined to have evaluable results; the EA of the evaluable results was 94.1%. There were no major or very major errors identified.

Table 4: Performance of Challenge Isolates, VITEK2 Manual Dilution Method

	Tot	No. EA	EA%	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Challenge	**75**	**74**	**98.7**	**17**	**16**	**94.1**	**71**	**94.7**	**1**	**71**	**4**	**0**	**0**

Challenge isolates interpreted using the VITEK 2 Compact and inoculated using the manual dilution method demonstrated an EA of 100.0% and a CA of 96.0% (Table 5). A total of 18 isolates were determined to have evaluable results; the EA of the evaluable results was 100%. There were no major or very major errors identified.

Table 5: Performance of Challenge Isolates, VITEK2 Compact, Manual Dilution Method

	Tot	No. EA	EA%	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Challenge	**75**	**75**	**100**	**18**	**18**	**100**	**72**	**96.0**	**1**	**71**	**3**	**0**	**0**

Only two resistant isolates were tested with this device, one clinical isolate and one challenge isolate. Due to the lack of available resistant isolates at the time of comparative testing the sponsor was asked to include the following limitation in their device labeling:

The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were not available at the time of comparative testing:

Tigecycline: Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Citrobacter koseri, Enterobacter aerogenes, Serratia marcescens

Trending. Analysis of trending of MIC values indicated that overall for all *Enterobacteriaceae* no trending was observed. However, when evaluated by species MICs for *K. pneumoniae* tended to be one dilution higher than the reference method and MICs for *S. marcescens* tended to be one dilution lower than the reference method. The following footnote to the performance table was added to the device labeling.

Overall VITEK 2 Tigecycline MICs showed no trending. However, compared to reference broth microdilution, K. pneumoniae results tended to be one dilution higher; results for S. marcescens tended to be one dilution lower.

b. Matrix comparison:

N/A

3. Clinical studies:

   a. Clinical Sensitivity:

   N/A

   b. Clinical specificity:

   N/A

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

   N/A

4. Clinical cut-off:

   N/A

5. Expected values/Reference range:

Table 6. Interpretive Criteria for Tigecycline (FDA Drug Label)

Organism	FDA Interpretive Criteria for Tigecycline MIC (µg/mL)		
	S	I	R
Enterobacteriaceae	**≤ 2**	**4**	**≥ 8**

N. Proposed Labeling:

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 supports a substantial equivalence decision.