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

A. 510(k) Number:

K183551

B. Purpose for Submission:

To obtain a substantial equivalence determination for Minocycline for susceptibility testing of gram-negative bacilli on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

C. Measurand:

Minocycline 0.5 – 32 µg/mL.

D. Type of Test:

Automated quantitative antimicrobial susceptibility test for minocycline

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK 2 AST-Gram Negative Minocycline (≤0.5 - ≥32 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(s):

   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 Gram-negative 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-negative bacilli to antimicrobial agents when used as instructed.

2. Indication(s) for use:

   VITEK 2 AST-Gram Negative Minocycline 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 Minocycline is a quantitative test. Minocycline 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:
   Acinetobacter spp.
   Klebsiella (Enterobacter) aerogenes
   Escherichia coli
   Klebsiella spp.

   The VITEK 2 Gram-negative 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-negative bacilli to antimicrobial agents when used as instructed.

3. Special conditions for use statement(s):

   For prescription use only

Limitation:

Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):
Minocycline: Shigella species

4. Special instrument requirements:

VITEK 2 and VITEK 2 Compact Systems, VITEK 2 Systems (PC) version 9.02 or higher

I. Device Description:

The VITEK 2 AST card is a miniaturized, abbreviated, and automated version of the doubling dilution technique for determining the minimal 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 (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 Minocycline has the following concentrations in the card: 1, 4, 8, and 16 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for VITEK 2 AST-GN Minocycline on the VITEK 2 card is ≤ 0.5 – ≥ 32 µg/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   VITEK 2 AST-GN Amikacin

2. Predicate 510(k) number(s):
   K172731

3. Comparison with predicate:

Similarities		
Item	**Device: VITEK 2 AST-GN Minocycline (K183551)**	**Predicate: VITEK 2 AST-GN Amikacin (K172731)**
Intended Use	VITEK 2 AST-Gram Negative Minocycline 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 Minocycline is a quantitative test. Minocycline 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: *Acinetobacter* spp. *K. (Enterobacter) aerogenes* *Escherichia coli* *Klebsiella* spp.	VITEK 2 AST Gram Negative Amikacin 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 Amikacin is a quantitative test. Amikacin 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: *Pseudomonas* spp. *Escherichia coli* *Proteus mirabilis* *Klebsiella* spp. *Enterobacter* spp. *Serratia* spp. *Acinetobacter* species *(*excluding *A. baumannii* Complex) In vitro data available but clinical significance is unknown: *Citrobacter freundii*
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	Standardized saline suspension of test organism	Same
Test Card	VITEK 2 Gram Negative Susceptibility Test Card	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Analysis Algorithm	Growth pattern analysis	Same

Similarities		
Item	**Device: VITEK 2 AST-GN Minocycline (K183551)**	**Predicate: VITEK 2 AST-GN Amikacin (K172731)**
Detection Method	Light optics using optical scanner	Same
Report	Automatically generated and contains the MIC value with an interpretive category (S, I, R) for each antimicrobial on the test card	Same

Differences		
Item	**Device: VITEK 2 AST-GN Minocycline (K183551)**	**Predicate: VITEK 2 AST-GN Amikacin (K172731)**
Antimicrobial Agent	Minocycline	Amikacin
Antimicrobial Concentrations	1, 4, 8, and 16 µg/mL	2, 4, 16, 48 µg/mL
Reporting Range	*Enterobacteriaceae* and *Acinetobacter* species ≤ 0.5 – ≥ 32 µg/mL	*Enterobacteriaceae*, *Pseudomonas* species ≤ 1 - ≥ 64 µg/mL *Acinetobacter* species ≤ 2 - ≥ 64 µg/mL
Analysis Algorithm	Unique to minocycline	Unique to amikacin

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

- FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)
- CLSI M07, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Tenth Edition" Vol. 32 No. 2 (January 2015)
- CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-Eighth Edition, Vol. 38 No. 3 (January 2018)

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 within the systems use visible light to directly measure organism growth within each of the 64 microwells. Transmittance optics are 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study for the VITEK 2 AST-GN Minocycline was conducted at three clinical sites using ten isolates from indicated species. Testing was performed on three separate days and in triplicate for a total of 270 data points. The ten isolates included *Klebsiella pneumoniae pneumoniae* (five isolates), *Klebsiella pneumoniae* (one isolate), *K.* (*Enterobacter*) *aerogenes* (three isolates), and *Escherichia coli* (one isolate). Inocula were prepared using both the auto-dilution and manual dilution methods on the VITEK 2 System. Inocula were prepared using the manual dilution method on the VITEK 2 Compact System. Intra-site and inter-site reproducibility was calculated based on MIC values falling within +/- one doubling dilution from the mode MIC value. Most of data points were on-scale and within ± one doubling dilution agreement as compared to the mode MIC. For cases where off-scale values were obtained reproducibility was calculated as best case and worst case as described in the AST Special Controls Guidance Document.

The overall reproducibility of the VITEK 2 System was 100% (100% worst case) and 100% (99.63% worst case) using the auto-dilution and manual dilution inoculum methods, respectively. All MIC results with the VITEK 2 Compact System using the manual inoculation method were on-scale and the overall reproducibility was 100%. The combined reproducibility results for all three sites were acceptable.

b. Linearity/assay reportable range:

Not applicable

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

Quality Control (QC) Testing
The FDA/CLSI recommended QC organism (*E. coli* ATCC 25922) was tested throughout the comparative testing at three study sites. This QC organism was tested a minimum of 20 times/site by both the VITEK 2 AST-GN Minocycline card and with the CLSI broth microdilution reference method.

Both the auto-dilution and the manual dilution methods for VITEK 2 and the manual dilution for VITEK 2 Compact gave the expected QC result >95% of the time. Overall, QC performance was acceptable. The QC results are summarized in Table 1.

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

		VITEK 2 Auto-Dilution		VITEK 2 Manual Dilution		VITEK 2 Compact Manual Dilution	
Organism	**Conc. (µg/mL)**	**Test**	**Reference**	**Test**	**Reference**	**Test**	**Reference**
E. coli ATCC 25922 Expected Range 0.25 – 1 µg/mL	≤0.03125						
	0.0625						
	0.125						
	0.25		77		62		62
	≤0.5*	115	22	90	19	90	19
	1		16		9		9
	2						
	4						
	8						
	16						
	32						
	≥64						

*The lowest dilution of the VITEK 2 AST-GN Minocycline MIC range is ≤0.5 µg/mL.

The expected range for *E. coli* ATCC 25922 with minocycline is 0.25 – 1 µg/mL; however, the reporting range of the VITEK 2 AST-GN Minocycline is ≤ 0.5 - ≥ 32 µg/mL (MIC results: ≤ 0.5, 1, 2, 4, 8, 16, and ≥ 32) and does not provide results lower than 0.5 µg/mL. All QC results for *E. coli* ATCC 25922 were off-scale for the VITEK 2 card at the ≤ 0.5 µg/mL dilution. The sponsor provided the following footnote to the *E. coli* ATCC 25922 expected range in the device labeling QC table:

> *The FDA/CLSI Broth Microdilution expected QC range = 0.25 – 1 µg/mL. Does not include the full recommended dilution range for QC testing.*

As an additional check of the reference method, two gram positive organisms were tested throughout the study at each clinical site. Isolates tested were *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213. All results were within the expected range.

Inoculum Density Control

The DensiCHEK Plus was used to standardize the inoculum to a 0.5 MacFarland 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 367 clinical isolates and 106 challenge isolates were evaluated. All isolates grew in the VITEK 2 AST card. Therefore, a total of 473 isolates had VITEK 2 AST results available.

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:

Testing of minocycline on the VITEK 2 AST-Gram Negative card was performed at three external sites and one internal site using VITEK 2 Systems (PC) version 9.02. Results obtained with the VITEK 2 AST-Gram Negative card were compared to results obtained with the CLSI broth microdilution reference method using direct colony suspension inoculation. The reference panels were inoculated with test organisms and incubated as outlined in the CLSI document M07-A10 at 35 ℃ for 16 – 20 hours for all organisms other than *Acinetobacter* spp., or at 35 ℃ for 20 - 24 hours for all *Acinetobacter* spp. organisms.

The VITEK 2 AST cards were inoculated with test organisms using the auto-dilution method (VITEK 2 System) and using the manual dilution method (VITEK 2 System 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 367 clinical isolates were evaluated (331 *Enterobacteriaceae* and 36 *Acinetobacter* spp.). All 367 isolates grew, and complete results were available for all isolates. A total of 238 (64.9%) isolates were fresh or recent isolates (tested within one year of isolation from clinical specimens) and 129 (35.1%) were stock isolates. The clinical study included species within *Enterobacteriaceae* that were not indicated in the FDA drug label for minocycline.

A total of 106 challenge organisms (80 *Enterobacteriaceae* and 26 *Acinetobacter* spp.) were evaluated at one external site. All isolates grew. The challenge set was tested with both the auto-dilution and manual dilution options on the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System. Challenge isolates included *Acinetobacter* spp. (26 isolates), *E. coli* (12 isolates), K. (Enterobacter) *aerogenes* (9 isolates), and *Klebsiella* spp. (59 isolates).

The combined data set of clinical and challenge isolates included 473 AST results (411 *Enterobacteriaceae* and 62 *Acinetobacter* spp.). A total of 112 (23.7%) resistant

isolates were tested among the clinical (n=56) and challenge (n=56) isolates.

The overall performance using the auto-dilution method of the VITEK 2 System demonstrated an EA of 97.0% and a CA of 93.7%. There was one major error (1/361 susceptible isolates, 0.3% error rate), one very major error (1/112 resistant isolates, 0.9% error rate), and 28 minor errors (28/473 total isolates, 5.9% error rate). The major error and very major error rates were acceptable. With *Enterobacteriaceae* isolates, performance was acceptable with an EA of 97.6% and a CA of 93.7%. With *Acinetobacter* spp. isolates, performance was acceptable with an EA of 93.5% and a CA of 93.5%. The performance based on combined clinical and challenge data was acceptable. The overall performance is shown in Table 2.

To address testing of non-indicated species the sponsor included the following statement in the Precautions section of the device labeling:

> *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.*

Table 2. Performance of Clinical and Challenge Isolates, VITEK 2 Auto-Dilution Method

Organism Type	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Min	Maj	Vmj
Enterobacteriaceae												
Clinical	331	324	97.9%	245	238	97.1%	308	93.1%	52	21	1	1
Challenge	80	77	96.3%	61	58	95.1%	77	96.3%	38	3	0	0
Combined	**411**	**401**	**97.6%**	**306**	**296**	**96.7%**	**385**	**93.7%**	**90**	**24**	**1**	**1**
***Acinetobacter* species**												
Clinical	36	33	91.7%	17	14	82.4%	33	91.7%	4	3	0	0
Challenge	26	25	96.2%	25	24	96.0%	25	96.2%	18	1	0	0
Combined	**62**	**58**	**93.5%**	**42**	**38**	**90.5%**	**58**	**93.5%**	**22**	**4**	**0**	**0**
All species												
Clinical	367	357	97.3%	262	252	96.2%	341	92.9%	56	24	1	1
Challenge	106	102	96.2%	86	82	95.3%	102	96.2%	56	4	0	0
Combined	**473**	**459**	**97.0%**	**348**	**334**	**96.0%**	**443**	**93.7%**	**112**	**28**	**1**	**1**

EA – Essential Agreement (± 1 dilution)
CA – Category Agreement
Eval – Evaluable isolates
R – Resistant isolates
Min – minor discrepancies
Maj – major discrepancies
Vmj – very major discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the VITEK card are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the VITEK card. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by the VITEK card.

Challenge Data – Auto and Manual Dilution

The challenge data set was evaluated at one site with both the auto-dilution and manual dilution options of the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System. The performance was acceptable. Overall performance is shown in Table 3, and performances with *Acinetobacter* spp. and *Enterobacteriaceae* isolates are shown in Table 4 and Table 5, respectively.

Table 3. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact – All Organisms

Dilution	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Min	Maj	Vmj
VITEK 2 System												
Auto	106	102	96.2	86	82	95.3	102	96.2	56	4	0	0
Manual	106	103	97.2	86	83	96.5	102	96.2	56	4	0	0
VITEK 2 Compact												
Manual	106	102	96.2	85	81	95.3	100	94.3	56	6	0	0

Table 4. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact - *Acinetobacter* spp.

Dilution	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Min	Maj	Vmj
VITEK 2 System												
Auto	26	25	96.2	25	24	96.0	25	96.2	18	1	0	0
Manual	26	26	100	25	25	100	25	96.2	18	1	0	0
VITEK 2 Compact												
Manual	26	25	96.2	25	24	96.0	25	96.2	18	1	0	0

Table 5. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact - *Enterobacteriaceae*

Dilution	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Min	Maj	Vmj
VITEK 2 System												
Auto	80	77	96.3	61	58	95.1	77	96.3	38	3	0	0
Manual	80	77	96.3	61	58	95.1	77	96.3	38	3	0	0
VITEK 2 Compact												
Manual	80	77	96.3	60	57	95.0	75	93.8	38	5	0	0

MIC Trends

An analysis of trending was conducted using the combined clinical and challenge data for each organism group. This trending calculation considers MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method regardless of whether the device MIC values are on-scale. 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.

Trending analysis results are shown in Table 6; results were stratified by species to assess species-related trends. Species for which the difference between the percentage of isolates with higher or lower readings was ≥30 with a statistically significant confidence interval were considered to show evidence of trending. Trending that provides higher or lower MIC values compared to the reference method is addressed in labeling.

When all species combined were assessed, no trending was observed overall. When results were stratified by species, trends for lower MIC values compared to the reference method were observed for *E. coli* and *S. marcescens*, and trends for higher MIC values compared to the reference method were observed for *K. oxytoca* and *C. freundii* (Table 6). The following footnote was added to performance table in the package insert to address trending:

"*VITEK 2 Minocycline MIC values tended to be in exact agreement or at least one doubling dilution lower when testing E. coli and S. marcescens compared to the reference broth micro-dilution. VITEK 2 Minocycline MIC values tended to be in exact agreement or at least one doubling dilution higher when testing K. oxytoca and C. freundii compared to the reference broth micro-dilution.*"

Table 6. MIC Trending Analysis of All Organisms (Clinical and Challenge)

Organism	Total Evaluable For Trending	≥1 Dilution Lower No. (%)	Exact No. (%)	≥1 Dilution Higher No. (%)	Percent Difference* (95% CI)	Trending Noted
E. coli	64	26 (40.6)	32 (50.0)	6 (9.4)	-31.25 (-44.5 to -16.5)	Yes
S. marcescens	19	7 (36.8)	11 (57.9)	1 (5.3)	-31.58 (-54.1 to -5.3)	Yes
C. freundii	7	1 (14.3)	1 (14.3)	5 (71.4)	57.14 (5.8 – 80.6)	Yes
K. oxytoca	23	2 (8.7)	11 (47.8)	10 (43.5)	34.78 (9.4 – 55.5)	Yes
All organisms assessed	368	104 (28.3)	186 (50.5)	78 (21.2)	-7.07 (-13.2 to -0.8)	No

***** A positive percent difference indicates a higher MIC value compared to the reference method. A negative percent difference indicates a lower MIC value compared to the reference method.

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:

Table 7. Interpretive Criteria for Minocycline (FDA STIC Webpage* and CLSI M100)

Organism	FDA Interpretive Criteria for Minocycline MIC (µg/mL)		
	S	I	R
Acinetobacter spp.	≤4	8	≥16
Enterobacteriaceae	≤4	8	≥16

* FDA STIC Webpage
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

O. Conclusion:

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