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

A. 510(k) Number:

K161437

B. Purpose for Submission:

To obtain a substantial equivalence determination for Cefotaxime 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 cefotaxime: 0.5, 2, 4, 8 and 32 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result reporting range for the card is ≤0.25 - ≥64 µg/mL.

D. Type of Test:

Automated quantitative antimicrobial susceptibility test for Cefotaxime

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:
VITEK®2 AST-GN Cefotaxime (≤ 0.25 - ≥ 64 µg/mL)
VITEK®2 AST Gram Negative Cefotaxime (≤ 0.25 - ≥ 64 µg/mL)

G. Regulatory Information:

1. Regulation section:

   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 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.

2. Indication(s) for use:

   VITEK®2 Gram Negative Cefotaxime 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 Cefotaxime is a quantitative test. Cefotaxime has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for the antimicrobial.

   Active in vitro and in clinical infections:
   Acinetobacter spp.
   Citrobacter spp.
   Enterobacter spp.
   Escherichia coli
   Klebsiella spp. (including Klebsiella pneumoniae)
   Proteus mirabilis
   Proteus vulgaris
   Providencia rettgeri
   Providencia stuartii
   Serratia marcescens

   In vitro data available but clinical significance is unknown:
   Providencia spp.
   Salmonella spp. (including Salmonella typhi)

   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.

3. Special conditions for use statement(s):

   Prescription use only

   The following limitations are included in the device labeling:

   > *Due to an insufficient number of P. vulgaris on-scale isolates available for comparative testing, the performance of VITEK2 Gram Negative Cefotaxime is unknown for this species with MICs of 1 to 4 µg/mL. Isolates with MICs of 1 to 4 µg/mL should be tested with an alternate method.*
   >
   > *Perform an alternate method of testing for the following antibiotic/organism combination(s): Cefotaxime: Shigella sp.*

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 Gram Negative Cefotaxime has the following concentrations in the card: 0.5, 2, 4, 8 and 32 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 Cefotaxime is ≤ 0.25 - ≥ 64 µg/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITEK 2 Gram Negative Ertapenem

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

   K152075

3. Comparison with predicate:

   Table 1. Comparison to the Predicate Device

Similarities		
Item	Device	Predicate VITEK2 Gram Negative Ertapenem K152075
Intended Use	VITEK 2 Gram Negative Cefotaxime is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK2 and VITEK2 Compact Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK2 Gram Negative Cefotaxime is a quantitative test. Cefotaxime 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. Citrobacter spp. Enterobacter spp. Klebsiella spp. (including K. pneumoniae)	VITEK 2 Gram Negative Ertapenem is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK2 and VITEK2 Compact Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK2 Gram Negative Ertapenem is a quantitative test. Ertapenem 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: *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* In vitro data available but

Similarities		
Item	Device	Predicate VITEK2 Gram Negative Ertapenem K152075
	Morganella morganii Proteus mirabilis Proteus vulgaris Providencia rettgeri Providencia stuartii Serratia marcescens In vitro data available but clinical significance unknown: Providencia spp. Salmonella spp. The VITEK2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK2 System 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.	clinical significance is unknown: *Citrobacter freundii* *Citrobacter koseri* *Enterobacter aerogenes* *Enterobacter cloacae* *Klebsiella oxytoca* (excluding ESBL producing isolates) *Morganella morganii* *Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Serratia marcescens* The VITEK2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK2 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.
Test Method	Automated quantitative antimicrobial susceptibility test for use with the VITEK and VITEK2 Compact Systems to determine the in vitro susceptibility of Gram negative bacilli.	Same
Inoculum	Saline suspension of organism	Same
Test Card	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 - Cefotaxime	Concentration of antimicrobial in the test wells of the VITEK® 2 AST card and the analysis algorithms are unique for each antimicrobial - Ertapenem
Antimicrobial Concentrations	0.5, 2, 4, 8 and 32 µg/mL	0.03, 0.12, 0.5, and 2 µg/mL
Reporting Range	≤ 0.25 - ≥ 64 µg/mL	≤0.12 - ≥ 8 µg/mL
Analysis algorithm	Unique to cefotaxime	Unique to Ertapenem

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

CLSI M100-S24: Performance Standards for Antimicrobial Susceptibility Testing
CLSI M07-A9: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow 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. <u>Analytical performance:</u>

   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 cloacae* (one isolate), *Serratia marcescens* (three isolates), *Enterobacter aerogenes* (one isolate), *Citrobacter freundii* (one isolate), *E. coli* (two isolates) and *Klebsiella pneumoniae pneumoniae* (two isolates). Inocula were prepared manually and using automatic dilution for

testing in the VITEK 2. Inocula were prepared manually for testing in the VITEK 2 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 VITEK 2 and automatic dilution, 269 of 270 results were on scale. Best case and worst case reproducibility was 99.63%.

Using VITEK 2 and manual dilution, all results were on scale and the reproducibility was 100%.

Using VITEK 2 Compact and manual dilution, all results were on scale and the reproducibility was 98.15%.

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 within the 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. During the course of the study only one clinical isolate failed to grow in the VITEK 2 Gram Negative Cefotaxime card. There were no growth failures with the challenge isolates.

Quality Control Testing. The CLSI-recommended QC organisms *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were evaluated using both the VITEK 2 Cefotaxime card and the reference method at each site using both the automatic dilution and the manual dilution for the VITEK 2 and using the manual dilution method for the VITEK 2 Compact.

The expected range for *E. coli* ATCC 25922 with cefotaxime is 0.03 – 0.12 µg/mL. The cefotaxime concentrations included in the VITEK 2 Cefotaxime card are 0.5, 2, 4, 8 and 32 µg/mL and the reporting range is ≤0.25 - ≥ 64 µg/mL. Therefore all results with this QC strain were off scale for the VITEK 2 and VITEK 2 Compact Systems and were reported as ≤ 0.25 µg/mL (Table 2). Even though *P. aeruginosa* is not a claimed organism for the VITEK 2 Cefotaxime, the *P. aeruginosa* ATCC 27853 strain was also tested and provided on-scale MIC values and 100% of the results were within the expected range (Table 2).

The sponsor included the following footnote to the QC table in the device labeling:

> *"The VITEK 2 AST-GN Cefotaxime test does not include the full CLSI/FDA-recommended dilution range for QC testing with E. coli ATCC 25922."*

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 – 0.12 µg/mL	≤0.015						
	0.03		27		24		22
	0.06		170		124		122
	0.12		26		17		17
	(≤)0.25*	223		165		161	
	0.5						
	1						
	2						
	4						
	8						
	16						
	32						
	64						
	≥ 128						
P. aeruginosa ATCC 27853 Expected Range 8 – 32 µg/mL	≤0.015						
	0.03						
	0.06						
	0.12						
	0.25						
	0.5						
	1						
	2						
	4						
	8	1	72	1	44	1	44
	16	218	146	155	113	148	111
	32	5	8	9	8	13	7
	64						
	≥ 128						

* Lowest value reported on the VITEK Card

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 bioMérieux VITEK 2 AST - Gram Negative card with cefotaxime were compared to results obtained with the CLSI frozen broth microdilution reference panel. The VITEK 2 AST-Gram Negative card with cefotaxime contains the following concentrations of cefotaxime: 0.5, 2, 4, 8 and 32 µg/mL (equivalent standard method concentration by efficacy in µg/mL) and the reporting range is ≤0.25 - ≥ 64 µg/mL. The frozen reference panel contained two-fold serial dilutions with a range of 0.015 to 256 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 521 *Enterobacteriaceae* clinical isolates were evaluated at four 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 (430 isolates, 82.5%); 91 isolates (17.5%) were stock isolates.

A total of 110 challenge isolates were tested at two sites. 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 and inoculated using the automatic dilution method, the combined results from clinical and challenge testing demonstrated a combined EA of 97.5% and CA of 97.8% (Table 3). A total of 83 isolates were determined to have evaluable results; the EA of the evaluable results was 86.7%. One clinical and one challenge isolate of *S. marcescens* were determined to be resistant by the reference method, but susceptible by VITEK 2, major errors; the sponsor included the following footnote to the performance table

in the device labeling:

> *"Overall error rates were acceptable; however two susceptible isolates of Serratia marcescens gave resistant results with VITEK 2 Cefotaxime, resulting in major errors."*

Two clinical isolates (one *E. cloacae* isolate and one *P. mirabilis*) were determined to be resistant by the reference method but susceptible by VITEK2, very major errors; analysis of trending showed that compared to the broth microdilution reference method, MICs for VITEK2 Cefotaxime tended to be at least one doubling dilution lower and may be responsible for the occurrence of the very major errors. A footnote to the performance table states:

> *Compared to the reference broth microdilution, results for Enterobacteriaceae and tended to be one dilution lower and may be responsible for very major errors with Proteus sp. and Enterobacter sp.*

For Proteus vulgaris, there wer no resistant isolates and no isolates with on-scale MIC values evaluated. The sponsor included the following limitation in the device labeling:

> *Due to an insufficient number of P. vulgaris on-scale isolates available for comparative testing, the performance of VITEK2 Gram Negative Cefotaxime is unknown for this species with MICs of 1 to 4 µg/mL. Isolates with MICs of 1 to 4 µg/mL should be tested with an alternate method.*

In addition, an insufficient number of *Shigella* species were evaluated; all *Shigella* isolates had MICs ≤ 0.12 µg/mL. The sponsor removed the claim for *Shigella* sp. and included the following limitation in the device labeling:

Limitation:

> *Perform an alternate method of testing for the following antibiotic/organism combination(s): Cefotaxime: Shigella spp."*

The performance based on clinical and challenge isolates 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	min	maj	vmj
Clinical	521	507	97.3	63	53	84.1	513	98.5	94	5	1	2
Challenge	110	108	98.2	20	19	95.0	104	94.5	17	5	1	0
Combined	631	615	97.5	83	72	86.7	617	97.8	111	10	2	2

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

Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of 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. 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.

Challenge isolates interpreted using the VITEK 2 and inoculated using the manual dilution method demonstrated an EA of 99.1% and a CA of 96.4% (Table 4). A total of 19 isolates were determined to have evaluable results; the EA of the evaluable results was 100.0%. There were no major or very major errors.

Table 4: Performance of Challenge Isolates, VITEK 2 Manual Dilution Method

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	min	maj	vmj
Challenge	110	109	99.1	19	19	100.0	106	96.4	17	4	0	0

Challenge isolates interpreted using the VITEK 2 Compact and inoculated using the manual dilution method demonstrated an EA of 99.1% and a CA of 95.5% (Table 5). A total of 19 isolates were determined to have evaluable results; the EA of the evaluable results was 94.7%. One *S. marcescens* challenge isolate was determined to be susceptible by the reference method but resistant by VITEK 2 Compact, a major error. This major error is addressed in the footnote to the performance table noted above.

Table 5: Performance of Challenge Isolates, VITEK 2 Compact, Manual Dilution Method

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	min	maj	vmj
Challenge	110	109	99.1	19	18	94.7	105	95.5	17	4	1	0

Trending. An analysis of trending of MIC values for all *Enterobacteriaceae* and *Acinetobacter* sp. indicated that compared to the broth microdilution reference method, MICs for VITEK2 Cefotaxime tended to be at least one doubling dilution lower. This trending calculation takes into account MIC values that are determined to be ≤ 1 or ≥ 1 doubling dilution compared to the reference method irrespective whether the device MIC values are on-scale or not. The sponsor added the following footnote to the performance table in the device labeling:

Compared to the reference broth microdilution, results for Enterobacteriaceae tended to be one dilution lower and may be responsible for very major errors with Proteus sp. and Enterobacter sp.

b. Matrix comparison:

N/A

3. Clinical studies:

a. Clinical Sensitivity:

N/A

b. Clinical specificity:

N/A

c. Other clinical supportive data:

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

Table 6. Breakpoints and Interpretive Categories for Cefotaxime (FDA Drug Label)

Organism	FDA Interpretive Criteria for Cefotaxime MIC (µg/mL)		
	S	I	R
Enterobacteriaceae *Acinetobacter spp.*	≤ 1	2	≥ 4

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.