510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K161217

B. Purpose for Submission:

To obtain a substantial equivalence determination for Ceftriaxone 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 Ceftriaxone: 0.12, 0.25, 1, 4 and 16µg/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 or qualitative antimicrobial susceptibility test for Ceftriaxone

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK®2 Gram Negative Ceftriaxone (≤ 0.25 - ≥64 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 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., *S. pneumoniae* and clinically significant yeast.

2. Indication(s) for use:

   VITEK®2 Gram Negative Ceftriaxone is designed for antimicrobial susceptibility testing of Gram negative bacilli. VITEK®2 Gram Negative Ceftriaxone is a quantitative test 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. Ceftriaxone 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 aerogenes
   Escherichia coli
   Klebsiella pneumoniae
   Klebsiella oxytoca
   Proteus mirabilis
   Serratia marcescens

   In vitro data available but clinical significance is unknown:
   Citrobacter freundii
   Citrobacter koseri (formerly Citrobacter diversus)
   Shigella species
   Providencia species (including Providencia rettgeri)
   Salmonella species (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., *S. pneumoniae* and clinically significant yeast.

3. Special conditions for use statement(s):

   Prescription use only

   The following limitations are included in the device labeling:

   - *Perform an alternate method of testing prior to reporting results for the following antibiotic/organism combination Ceftriaxone/Proteus vulgaris*

   - *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 comparable testing. Ceftriaxone: Shigella species, Providencia rettgeri, and Salmonella species.*

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 test card contains 64 microwells. A control well containing only culture medium is included on all cards, with the remaining wells containing premeasured amounts of a specific antimicrobial agent in a culture medium base. A suspension of organisms from a pure culture is prepared in a tube containing 0.45-0.5% sterile saline and standardized to a McFarland 0.5 using the DensiCHEK Plus™. The VITEK 2 System automatically fills seals and places the card into the incubator/reader; manual methods can also be used for the inoculation of test cards for use in the VITEK 2 System. The VITEK 2 Compact has a manual filling and sealing operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time (up to 18 hours). 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-Gram Negative Ceftriaxone has the following concentrations in the card: 0.12, 0.25, 1, 4 and 16µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is ≤ 0.25 - ≥64 µg/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITEK®2 AST-GN Doxycycline

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

   K121546

3. Comparison with predicate:

Table 1: Comparison with the Predicate Device

Similarities		
Item	Device VITEK®2 AST-GN Ceftriaxone	Predicate VITEK®2 AST-GN Doxycyline (K121546)
Intended Use	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.	Same
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 organisms	Same

Differences		
Item	Device	Predicate
Antimicrobial	Ceftriaxone	Doxycycline
Antimicrobial Concentration	0.12, 0.25, 1, 4 and 16	1, 4, and 16
Reading Algorithm	Growth pattern analysis-Unique to Ceftriaxone	Discriminate Analysis - Unique to Doxycycline

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

CLSI M100-S25 Performance Standards for Antimicrobial Susceptibility Testing
CLSI M07-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically

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 aerogenes* (one isolate), *E. coli (*two isolates*)*, *Klebsiella pneumoniae* (four isolates), *Serratia marcescens* (two isolates) and *Citrobacter freundii (*one isolate). Inocula were prepared both manually and using automatic dilution for testing in the VITEK 2. Inocula were prepared manually for testing in the VITEK 2 Compact. The modal 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 automatic and manual dilution options, the best and worst case results were 100%. All results were on scale.

Using VITEK 2 Compact and manual dilution, best and worst case reproducibility was 98.15%. All results were on scale.

The reproducibility results were acceptable.

b. Linearity/assay reportable range:

Not Applicable

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 FDA recommended QC organisms (*E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) were tested using both the VITEK 2 card and the reference method at each site. Both the automatic dilution and manual dilution methods were used for the VITEK 2 and the manual dilution method was used for the VITEK 2 Compact.

The expected range for *E. coli* ATCC 25922 with Ceftriaxone is 0.03 – 0.12 µg/mL. Even though the Ceftriaxone concentrations included in the VITEK 2 AST-Gram Negative card are 0.12, 0.5, 1, 4 and 16µg/mL, the reporting range is ≤0.25 - ≥64 µg/mL. Therefore, all results for the QC strain were off-scale for the VITEK 2 and VITEK 2 Compact Systems as both VITEK systems report the lowest end of the scale as ≤0.25 µg/mL (Table 2). However, *Pseudomonas aeruginosa* ATCC 27853 was also tested to verify the performance of the device (Table 2) and all results were on-scale. All VITEK results with this organism were acceptable as they were within the expected range of 8-64 µg/mL.

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 to 0.12 µg/mL	≤0.015625						
	0.03125		47		41		40
	0.0625		162		117		114
	0.125		14		7		7
	≤0.25*	223	NA	165	NA	161	NA
	0.5						
	1						
	2						
	4						
	8						
	16						
	32						
	64						

		VITEK 2 Automatic-Dilution		VITEK 2 Manual Dilution		VITEK 2 Compact Manual Dilution	
Organism	**Conc. (µg/mL)**	**Test**	**Ref.**	**Test**	**Ref.**	**Test**	**Ref.**
	≥128						
P. aeruginosa (ATCC 27853) Expected Range: 8-64 µg/mL	≤0.015625						
	0.03125						
	0.0625						
	0.125						
	0.25						
	0.5						
	1						
	2						
	4		1		1		1
	8	54	161	46	112	36	113
	16	157	55	110	47	117	43
	32	7	6	4	4	3	4
	64	1		5		6	1
	≥128						

***** *The lowest end point of the VITEK 2 Ceftriaxone MIC range is ≤0.25 µg/mL. Obtaining this value was considered as an indicator that the quality control test results were acceptable.*

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:

Results obtained with the bioMérieux VITEK 2 AST - Gram Negative card with Ceftriaxone were compared to results obtained with the CLSI broth microdilution reference panel. The VITEK 2 AST-Gram Negative card with Ceftriaxone contains the following concentrations of Ceftriaxone: 0.12, 0.25, 1, 4 and 16 µg/mL (equivalent standard method concentration by efficacy in µg/mL) and the reporting range is ≤ 0.25 - ≥64 µg/ml. The reference panel contained two-fold serial dilutions with a range of 0.0156 to 128 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-A10.

A total of 410 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 (343isolates, 83.6%); 67 isolates (16.3%) were stock isolates.

A total of 71challenge isolates were tested at two sites (one internal and one external site). In response to a request from FDA, 31 additional challenge isolates were evaluated internally for a total of 102 challenge isolates. Results from these additional isolates are included in the challenge isolate results provided in Table 3. The challenge set was tested with both card inoculation options (automatic and manual dilution methods) on the VITEK 2 System and with the manual dilution on the VITEK 2 COMPACT system. The performance is shown in Table 3.

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

	EA Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	min	maj	vmj
Clinical	410	402	98.0	21	16	76.2	409	99.8	38	0	1	0
Challenge	102	97	95.1	24	19	79.2	98	96.1	13	4	0	0
Combined	512	499	97.5	45	35	77.8	507	99.0	51	4	1	0

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.

The overall performance using the VITEK 2 System and inoculated using the automatic dilution method was acceptable, with an EA of 97.5% and CA of 99.0%, and a minor discrepancy rate of 0.8% (4/512) and a major error discrepancy rate of 0.2% (1/458). There were no very major errors (Table 3).

Performance of *Proteus vulgaris*:
The performance of *Proteus vulgaris* did not meet the performance criteria for Essential Agreement according to the AST Class II Special Controls Guidance

Document: Antimicrobial Susceptibility Test (AST) Systems. The AST results for Ceftriaxone with *Proteus vulgaris* will be suppressed from reporting in the VITEK 2 system. This was addressed in the labeling by adding the following limitation in the labeling:

> *"Perform an alternate method of testing prior to reporting results for the following antibiotic/organism combination: Ceftriaxone/Proteus vulgaris".*

Evaluable Isolates:
A large percentage of the clinical and challenge isolates tested in the evaluation of Ceftriaxone were either highly susceptible or highly resistant resulting in acceptable overall EA. A total of 45 isolates were determined to have evaluable results. Of these isolates, 35 were within essential agreement (EA) for a percent EA of evaluable isolates of 77.8%. Based on the limited data with evaluable isolates, the following footnote pertinent to Ceftriaxone is added in the labeling (Product Information Manual):

> "*Due to an insufficient number of on-scale isolates available for comparative testing, the performance of VITEK 2 Gram Negative Ceftriaxone is unknown for isolates with MICs in the range of 1 to 4 µg/mL. If critical to patient care, isolates with MICs of 1 to 4 µg/mL should be retested using another method".*

Resistant Organisms:
A total of 51 resistant organisms were identified out of 512 organisms tested (9.9%) in the combined challenge and clinical study of Ceftriaxone for the VITEK 2 with automatic dilution. However, the following organisms had no resistant isolates available during the comparative study: *Shigella* species, *Providencia rettgeri*, *Salmonella* species, and *Shigella* species. This was addressed by adding the following limitation in the package insert:

> *"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. Ceftriaxone: Shigella species, Providencia rettgeri, Salmonella species, and Shigella species."*

Challenge Data-Manual Dilution:
The challenge set of 102 isolates evaluated using the VITEK 2 and inoculated using the manual dilution method demonstrated an EA and CA of 96.1 % (Table 4). A total of 24 isolates were determined to have evaluable results. Of these isolates, 20 were within essential agreement (EA) for a percent EA of evaluable isolates of 83.3%.The results were acceptable.

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

	EA Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	min	maj	vmj
Challenge	102	98	96.1	24	20	83.3	98	96.1	13	3	1	0

VITEK 2 COMPACT:
The challenge set of 102 isolates was also evaluated using the VITEK 2 Compact and inoculated using the manual dilution method demonstrated an EA of 96.1% and CA of 97.1% (Table 5). A total of 23 isolates were determined to have evaluable results. Of these isolates, 19 were within essential agreement (EA) for a percent EA of evaluable isolates of 82.6%.

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

	EA Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	min	maj	vmj
Challenge	102	98	96.1	23	19	82.6	99	97.1	13	2	1	0

Even though the EA of evaluable was low, the overall performance of the VITEK 2 Compact (manual dilution) was considered acceptable based on the acceptable performance in overall EA, the reproducibility study, and QC (Table 2)

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 6: Interpretive Criteria for Ceftriaxone (FDA Drug Label)

Organism	FDA Interpretive Criteria for Ceftriaxone MIC (µg/mL)		
	S	**I**	**R**
Enterobacteriaceae	≤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.