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

A. 510(k) Number:

K152075

B. Purpose for Submission:

To obtain a substantial equivalence determination for Ertapenem 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 ertapenem: 0.03, 0.12, 0.5 and 2 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result reporting range for the card is ≤0.12 - ≥8 µg/mL.

D. Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test for Ertapenem

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:
VITEK®2 AST-Gram Negative Ertapenem (≤0.12 - ≥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 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 Ertapenem 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 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 the antimicrobial.

   Active in vitro and in clinical infections:
   Escherichia coli
   Klebsiella pneumoniae
   Proteus mirabilis

   In vitro data available but 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

3. Special conditions for use statement(s):

   Prescription use only

   The following limitation is included in the device labeling:

   "Due to an insufficient number of on-scale isolates available for comparative testing, the

performance of VITEK 2 Gram Negative Ertapenem is unknown for isolates with MICs in the range of 0.25 – 0.5 µg/mL. To avoid the occurrence of very major errors, isolates with MICs of 0.25 and 0.5 µg/mL should be retested using another method."

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 organism 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-GN Ertapenem has the following concentrations in the card: 0.03, 0.12, 0.5 and 2 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is ≤0.12 - ≥8 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 Ertapenem	Predicate VITEK®2 AST-GN Doxycyline K121546
Intended Use	*VITEK®2 Gram Negative Ertapenem is designed for antimicrobial susceptibility*	VITEK®2 Gram Negative Doxycycline is designed for antimicrobial susceptibility

Similarities		
Item	Device VITEK®2 AST-GN Ertapenem	Predicate VITEK®2 AST-GN Doxycyline K121546
	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 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 the antimicrobial. *<u>Active in vitro and in clinical infections</u>:* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *<u>In vitro data available but clinical significance is unknown:</u>* *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 VITEK®2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK®2 Systems for the automated quantitative or	testing of Gram Negative Bacilli. VITEK 2 GN Doxycline 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. Doxycline has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial. *<u>Active in vitro and in clinical infections</u>:* *Acinetobacter* species *Enterobacter aerogenes* *Escherichia coli* *Klebsiella* species *Shigella* species 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.

Similarities		
Item	Device VITEK®2 AST-GN Ertapenem	Predicate VITEK®2 AST-GN Doxycyline K121546
	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®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	Concentration of antimicrobial in the test wells of the VITEK®2 AST card and the analysis algorithms are unique for each antimicrobial. Ertapenem	Concentration of antimicrobial in the test wells of the VITEK®2 AST card and the analysis algorithms are unique for each antimicrobial Doxycycline
Reading Algorithm	Unique to Ertapenem	Unique to Doxycycline

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. 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* (four isolates), *E. coli* (one isolate), *Klebsiella pneumoniae* (three isolates) and *Serratia marcescens* (two isolates). 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 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, all results were on scale and the reproducibility was 100%.

Using VITEK 2 and manual dilution, best case reproducibility was 100%; worst case reproducibility was 99.3%.

Using VITEK 2 Compact and manual dilution, best case reproducibility was 100%; worst case reproducibility was 98.9%

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 ertapenem is 0.004 – 0.015 µg/mL. Even though the ertapenem concentrations included in the VITEK 2 AST-Gram Negative card are 0.03, 0.12, 0.5 and 2 µg/mL, the reporting range is ≤0.12 - ≥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 ≤0.12 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 bioMérieux's internal QC processes and analysis of growth patterns assure that the device was manufactured correctly. No other QC strains suitable for the *Enterobacteriaceae* claim could be identified that would cover the expected ertapenem MIC ranges based on CLSI or FDA drug label. Therefore, there was no specific recommendation for any additional QC strains to be tested. Furthermore, the sponsor included the following footnote to the QC table in the device labeling:

"The VITEK 2 card does not include the full CLSI/FDA-recommended dilution ranges for QC testing of ertapenem."

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: 0.004 – 0.015 µg/mL	≤0.0019						
	0.004		8		6		6
	0.008		239		177		173
	0.015		5		3		3
	0.03						
	0.06						
	≤0.125*	252		186		182	
	0.25						
	0.5						
	1						
	2						
	4						
	8						
	≥16						

* The lowest end point of the VITEK 2 MIC range is ≤0.12 µg/mL. Obtaining this value was considered as an indicator that the quality control test 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 bioMérieux VITEK 2 AST - Gram Negative card with ertapenem were compared to results obtained with the CLSI frozen broth microdilution reference panel. The VITEK 2 AST-Gram Negative card with ertapenem contains the following concentrations of ertapenem: 0.03, 0.12, 0.5 and 2 µg/mL (equivalent standard method concentration by efficacy in µg/mL) and the reporting range is ≤0.12 - ≥8 µg/mL. The frozen reference panel contained two-fold serial dilutions with a range of 0.002 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 541 *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 (408 isolates, 75.4%); 122 isolates (24.6%) were stock isolates.

A total of 136 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 97.9% and CA of 97.9% (Table 3). A total of 61 isolates were determined to have evaluable results; the EA of the evaluable results was 77.0%. One challenge isolate was determined to be resistant by the reference method, but susceptible by VITEK 2, a very major error. 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	min	maj	vmj
Clinical	541	534	98.7	21	14	66.7	539	99.6	63	2	0	0
Challenge	136	129	94.9	40	33	82.5	124	91.2	16	10	1	1
Combined	677	663	97.9	61	47	77.1	663	97.9	79	12	1	1

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 94.1% and a CA of 97.7% (Table 4). A total of 38 isolates were determined to have evaluable results; the EA of the evaluable results was 78.9%. Two challenge isolates were determined to be resistant by the reference method, but susceptible by VITEK 2, 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	136	128	94.1	38	30	78.9	125	91.9	16	9	0	2

Challenge isolates interpreted using the VITEK 2 Compact and inoculated using the manual dilution method demonstrated an EA of 94.1% and a CA of 91.2% (Table 5). A total of 39 isolates were determined to have evaluable results; the EA of the evaluable results was 79.5%. One challenge isolate was determined to be resistant by the reference method but susceptible by VITEK 2 Compact, a very major error.

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	136	128	94.1	39	31	79.5	124	91.2	16	11	0	1

A large percentage of the clinical and challenge isolates tested in the evaluation of ertapenem were either highly susceptible or highly resistant resulting in acceptable overall EA. Among the evaluable VITEK 2 MIC results, 9 of 61 results (14.8%) were two or three dilutions lower than results obtained with the reference method; an insufficient number of isolates with on-scale results were available for additional testing to further evaluate the EA of evaluable isolates. In order to address the possibility of obtaining very major errors with VITEK 2 results that were two to three dilutions lower than what would be obtained with the reference method, the following limitation was added indicating that isolates with MICs of 0.25 or 0.5 µg/mL should be tested by an alternative method.

"Due to an insufficient number of on-scale isolates available for comparative testing, the performance of VITEK 2 Gram Negative Ertapenem is unknown for isolates with MICs in the range of 0.25 – 0.5 µg/mL. To avoid the occurrence of very major errors, isolates with MICs of 0.25 and 0.5 µg/mL should be retested using another method."

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 Ertapenem (FDA Drug Label)

Organism	FDA Interpretive Criteria for Ertapenem MIC (µg/mL)		
	S	I	R
Enterobacteriaceae	≤0.5	1	≥2

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.