



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

I Background Information:

A 510(k) Number

K211136

B Applicant

bioMérieux, Inc

C Proprietary and Established Names

VITEK 2 AST-Gram Negative Imipenem/Relebactam (<0.25/4 - >16/4 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LON, LTW, LTT	Class II	21 CFR 866.1645 - Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To modify the indications for use for imipenem/relebactam to include a new indicated species, *Acinetobacter calcoaceticus-baumannii* complex.

B Measurand:

Imipenem/Relebactam ($\leq 0.25/4$ - $\geq 16/4$ µg/mL)

C Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

VITEK 2 AST-Gram Negative Imipenem/Relebactam 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 Imipenem/Relebactam is a quantitative test. Imipenem/Relebactam 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 calcoaceticus-baumannii complex
Klebsiella (Enterobacter) aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Citrobacter freundii
Klebsiella oxytoca

In vitro data are available. but clinical significance is unknown:

Citrobacter koseri
Enterobacter asburiae

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.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Limitation:

Perform and alternative method of testing prior to reorting or results for the following antibiotic/organism combination(s): Imipenem/Relebactam: Serratia marcescens

D Special Instrument Requirements:

VITEK 2 and VITEK 2 Compact Systems using VITEK 2 Systems 9.03 software

IV Device/System Characteristics:

A 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 (or allow operator to manually) 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. 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 antimicrobial 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-Gram Negative Imipenem/Relebactam has the following concentrations of imipenem/relebactam in the card: 0.25/4, 1/4, 4/4, and 16/4 µg/mL (equivalent standard method concentration by efficacy in µg/mL); the content of relebactam is fixed at 4 µg/mL in each dilution. The imipenem/relebactam MIC result range for the VITEK 2 is $\leq 0.25/4$ to $\geq 16/4$ µg/mL. For *Acinetobacter calcoaceticus-baumannii* complex, the VITEK 2 system is capable of reporting the following MIC results: $\leq 0.25/4$, 0.5/4, 1/4, 2/4, 4/4, 8/4 and $\geq 16/4$ µg/mL for the AST-Gram Negative Imipenem/relebactam test.

B Principle of Operation:

The VITEK 2 and VITEK 2 Compact Systems utilize automated growth-based detection using attenuation of light measured by an optical scanner. The optics in the systems use visible light to directly measure organism growth within each of the 64 micro-wells. Transmittance optics is 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 determine 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):

VITEK 2 AST-Gram Negative Imipenem/Relebactam ($\leq 0.25/4$ - $\geq 16/4$ µg/mL)

B Predicate 510(k) Number(s):

K193572

C Comparison with Predicate(s):

Device & Predicate Device(s):	<u>Device</u> K211136	<u>Predicate</u> K193572
Device Trade Name	VITEK 2 AST-Gram Negative Imipenem/Relebactam	VITEK 2 AST-Gram Negative Imipenem/Relebactam
General Device Characteristic Similarities		
Intended Use/Indications For Use	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.	Same
Test Method	Automated quantitative antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems to determine the <i>in vitro</i> susceptibility of Gram-negative organisms	Same
Inoculum	Standardized saline suspension of test organism	Same
Antimicrobial Agent	Imipenem/relebactam	Same
Incubation	35 °C; 16-24 hours	Same
Test Card	VITEK 2 Gram Negative Susceptibility Test Card	Same
Instrument	VITEK 2 and VITEK 2 Compact	Same
Analysis Algorithm	Growth pattern analysis	Same
Antimicrobial Concentration	0.25/4, 1/4, 4/4 and 16/4 µg/mL	Same
Reporting Range	≤0.25/4 to ≥16/4 µg/mL	Same

General Device Characteristic Differences		
Indicated organisms	<i>C. freundii</i> , <i>C. koseri</i> , <i>E. asburiae</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>K. aerogenes</i> , <i>K. oxytoca</i> , <i>K.</i> <i>pneumoniae</i> , <i>P.</i> <i>aeruginosa</i> , <i>Acinetobacter</i> <i>calcoaceticus-</i> <i>baumannii</i> complex	<i>C. freundii</i> , <i>C. koseri</i> , <i>E. asburiae</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>K. aerogenes</i> , <i>K. oxytoca</i> , <i>K.</i> <i>pneumoniae</i> , <i>P.</i> <i>aeruginosa</i>

VI Standards/Guidance Documents Referenced:

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, 11th ed. 2018

CLSI M100, Performance Standards for Antimicrobial Susceptibility Testing, 29th ed. 2019

CLSI M100, Performance Standards for Antimicrobial Susceptibility Testing, 30th ed. 2020

VII Performance Characteristics:

A Analytical Performance:

1. Precision/Reproducibility:

No new reproducibility study was needed since there was no change in the design of the device. All data previously evaluated during review of K193572 was acceptable. Reproducibility testing for the VITEK 2 AST-Gram Negative Imipenem/Relebactam was performed in support of clearance of K193572 with a 10-isolate panel composed of species indicated in the drug label. Testing was performed at three external sites. Reproducibility was evaluated for both of the VITEK 2 inoculation options and for the VITEK 2 Compact.

2. Linearity:

Not Applicable

3. Analytical Specificity/Interference:

Not Applicable

4. Assay Reportable Range:

Not Applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Testing of *Acinetobacter calcoaceticus-baumannii* complex isolates with the VITEK 2 AST-Gram Negative Imipenem/Relebactam took place at the time of testing *Enterobacterales* and *P. aeruginosa* isolates in support of clearance of K193572. The QC results were acceptable.

At the time of testing for K193572, the CLSI recommended QC strains, *K. pneumoniae* ATCC BAA-1705 and *K. pneumoniae* ATCC BAA-2814 were tested a sufficient number of times (at least 20 times/site) using both the VITEK 2 card and the broth microdilution (BMD) reference method. Because of the device design, the acceptable MIC ranges for CLSI-recommended QC strains were partially off-scale. Therefore, there was a need to validate a new QC strain to satisfy the QC requirements. The sponsor conducted a study to validate a novel *P. aeruginosa* strain (bioMérieux strain 105617) for use as an on-scale QC strain for imipenem/relebactam. The strain subsequently was submitted to ATCC and is cataloged as *P. aeruginosa* ATCC BAA-3144. Testing with this strain under K193572 provided results within the expected QC range for >95% of tests.

Subsequent to the clearance of K193572, the expected QC range for the CLSI-recommended strain *K. pneumoniae* ATCC BAA-2814 was modified from a range of 0.06/4 – 0.25/4 µg/mL to a range of 0.06 – 0.5/4 µg/mL (change first implemented in CLSI document M100 30th Edition). The results obtained with this QC strain during testing for K193572 reanalyzed using the revised expected QC range are shown in Table 1 below.

Table 1. Results of QC Testing with the Revised QC Range for *K. pneumoniae* ATCC BAA-2814^a

Organism	Conc. (µg/mL)	VITEK 2				VITEK 2 Compact	
		Auto-Dilution		Manual Dilution		Manual Dilution	
		Reference	Test	Reference	Test	Reference	Test
<i>K. pneumoniae</i> ATCC BAA-2814	≤0.008	-	NA ^b	-	NA ^b	-	NA ^b
	0.03	-	NA	-	NA	-	NA
	0.06	6	NA	4	NA	4	NA
	0.12	92	NA	70	NA	70	NA
	0.25	18	NA	14	NA	14	NA
	≤0.25 ^b	-	120	-	88	-	89
	0.5	5	-	4	-	4	-
	1	1	-	1	-	1	-
	≥2	-	-	-	-	-	-

^a Data from K193572 reanalyzed with the revised expected QC range

^b The lowest concentration of imipenem/relebactam on the VITEK 2 card is 0.25/4 µg/mL. Obtaining this value was considered an indicator that the quality control test results were acceptable. The sponsor included a footnote to the Quality Control table indicating that the VITEK 2 AST-Gram Negative Imipenem/Relebactam panel does not include the full CLSI-recommended dilution range for QC testing with this organism.

Integrity Check: In support of clearance of K193572 *K. pneumoniae* ATCC BAA-1705 was tested with imipenem alone as in integrity check for the plasmid encoding the β-lactamase gene.

Inoculum Density. The DensiCHECK Plus was used for the preparation of inoculum and the instrument was standardized daily. All recorded calibration values were within acceptable parameters.

Purity Checks. Purity checks were performed on all isolates tested. Only results from pure cultures were evaluated.

Growth Failure. There were no instances of growth failure during the evaluation of imipenem/relebactam.

6. Detection Limit:
Not Applicable

7. Assay Cut-Off:
Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of imipenem/relebactam with isolates belonging to the *Acinetobacter calcoaceticus-baumannii* complex was performed at three external sites and one internal site. Results obtained with VITEK 2 AST-Gram Negative Imipenem/Relebactam were compared to results obtained with the CLSI broth microdilution reference panel. The MIC result range for the VITEK 2 AST-Gram Negative Imipenem/Relebactam is $\leq 0.25/4$ to $\geq 16/4$ $\mu\text{g/mL}$ for all species. The testing conditions for the reference method consisted of the following:

- Medium – Cation Adjusted Mueller Hinton broth
- Inoculum – Direct colony suspension
- Incubation - 35° C, 16 to 24 hours

The VITEK 2 cards were inoculated with test organisms using the auto-dilution method (VITEK 2) and using the manual dilution method (VITEK 2 and VITEK 2 Compact). All test inocula used for the VITEK 2 AST cards and the reference method were standardized using the DensiCHECK Plus instrument.

A total of 32 clinical isolates of *Acinetobacter calcoaceticus-baumannii* complex, were evaluated: 9 isolates (28.1%) were considered contemporary isolates and 23 (71.9%) were stock isolates. Isolates included: *Acinetobacter baumannii* (20 isolates), and *Acinetobacter baumannii* complex (12 isolates). In addition, 24 challenge isolates of *Acinetobacter calcoaceticus-baumannii* complex were evaluated. Isolates included: *Acinetobacter baumannii* (10 isolates), *Acinetobacter baumannii* complex (13 isolates) and *Acinetobacter calcoaceticus* (1 isolate).

For *Acinetobacter calcoaceticus-baumannii* complex evaluated using VITEK 2 and autodilution, the combined clinical and challenge EA and CA were acceptable at 98.2% with all errors being minor (i.e. no major or very major errors). A total of 35 resistant strains were evaluated demonstrating the ability of the assay to detect resistance in this complex. (Table 2)

Table 2. AutoDilution: Performance of *Acinetobacter calcoaceticus-baumannii* Complex

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
<i>Acinetobacter calcoaceticus-baumannii</i> Complex^a													
Clinical	32	31	96.9	2	1	50.0	32	100	19	13	0	0	0
Challenge	24	24	100	8	8	100	23	95.8	16	8	1	0	0
Total	56	55	98.2	10	9	90.0	55	98.2	35	21	1	0	0

^a Includes *A. baumannii*, *A. baumannii* complex and *A. calcoaceticus*

EA – Essential Agreement
 CA – Category Agreement
 EVAL – Evaluable Isolates
 R – Resistant Isolates

min – minor errors
 maj – major errors
 vmj – very major errors
 S – Susceptible Isolates

Essential agreement (EA) occurs when the result of the reference method and that of the VITEK 2 AST-Gram Negative imipenem/relebactam 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 2 AST-Gram Negative imipenem/relebactam. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by VITEK 2 AST-Gram Negative Meropenem

For *Acinetobacter calcoaceticus-baumannii* complex evaluated using manual dilution with VITEK 2 and VITEK 2 Compact, EA and CA were acceptable at 100% with no major, very major or minor errors. (Table 3).

Table 3. Manual Dilution: Performance of *Acinetobacter calcoaceticus-baumannii* Complex

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
<i>Acinetobacter calcoaceticus-baumannii</i> Complex^a													
VITEK 2	24	24	100	8	8	100	24	100	16	8	0	0	0
Compact	24	24	100	8	8	100	24	100	16	8	0	0	0

^a Includes *A. baumannii*, *A. baumannii* complex and *A. calcoaceticus*

The performance of VITEK 2 AST-Gram Negative Imipenem/Relebactam with *Acinetobacter calcoaceticus-baumannii* complex using both autodilution (VITEK 2) and manual dilution (VITEK 2 and VITEK 2 Compact) is acceptable.

Subsequent to clearance of K193572, the imipenem/relebactam drug label was revised to include *S. marcescens* as a species for which the drug was shown to have in vitro and clinical activity. Testing of *S. marcescens* showed low performance on VITEK 2 systems. To address testing with this drug/organism combination the sponsor included the following limitation in the device labeling:

Perform and alternative method of testing prior to reporting or results for the following antibiotic/organism combination(s): Imipenem/Relebactam: Serratia marcescens

MIC Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained from the VITEK 2 auto-dilution method for each organism group. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method irrespective of whether the device MIC values are on-scale or not. 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.

Organism groups for which the difference between the percentage of isolates with higher vs. lower readings was > 30% and for which the confidence interval was determined to be statistically significant were considered to show evidence of trending. Trending that showed higher or lower MIC values compared to the reference is addressed in the labeling.

Evaluation of results for *Acinetobacter calcoaceticus-baumannii* Complex using autodilution on VITEK 2 showed that a majority of isolates provided MICs were not evaluable for trending due to the majority of the data being off-scale; however, the few evaluable results indicate a trend toward lower MIC results with the limited number of isolates available for trending analysis. (Table 4).

Table 4. Trending Observed for *Acinetobacter calcoaceticus-baumannii* complex

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
<i>Acinetobacter calcoaceticus-baumannii</i> complex.	15	10 (66.7)	5 (33.3)	0	-66.7 (-84.8 to -34.4)	Yes

The sponsor added the trending results for *Acinetobacter calcoaceticus-baumannii* complex to the current trending footnote to the performance table in the device labeling (additions for *Acinetobacter calcoaceticus-baumannii* complex in bold font):

*A trending analysis was conducted using combined data (clinical and challenge) for Enterobacteriaceae and Pseudomonas aeruginosa and **Acinetobacter calcoaceticus-baumannii complex**. This trending analysis determined the VITEK 2 Imipenem/Relebactam, when compared to the reference broth microdilution, tended to be at least one doubling dilution lower for Citrobacter koseri, **Acinetobacter calcoaceticus-baumannii complex** and Klebsiella pneumoniae, and at least one doubling dilution higher for Enterobacter cloacae.*

2. Matrix Comparison:
Not applicable

C Clinical Studies:

1. Clinical Sensitivity:
Not Applicable

2. Clinical Specificity:
Not Applicable
3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):
Not Applicable

D Clinical Cut-Off:
Not Applicable

E Expected Values/Reference Range:

Table 5. FDA-Identified Interpretive Criteria for Imipenem/Relebactam^a

Organism	Interpretive Criteria for Imipenem/Relebactam (µg/mL)		
	Susceptible	Intermediate	Resistant
<i>Enterobacteriales</i>	≤1/4	2/4	≥4/4
<i>P. aeruginosa</i>	≤2/4	4/4	≥8/4
<i>Acinetobacter calcoaceticus-baumannii</i> complex	≤2/4	4/4	≥8/4

^a [FDA STIC Webpage](#)

VIII Proposed Labeling:

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

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm>). The protocol outlined the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate the VITEK 2 AST-GN Imipenem/relebactam when revised breakpoints for imipenem/relebactam are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, bioMérieux will update the imipenem/relebactam device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.