510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K222378

B Applicant

bioMérieux, Inc.

C Proprietary and Established Names

VITEK 2 AST-Gram Negative Levofloxacin (≤0.125 - ≥8 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645 - Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System	MI - Microbiology
LTT	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LTW	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To update the VITEK 2 AST Gram Negative Levofloxacin (≤0.125 - ≥8) device labeling to include updated FDA-recognized breakpoints for Enterobacterales and *Pseudomonas aeruginosa*, include and report the susceptibility of *Salmonella* spp. as listed on the FDA Susceptibility Test Interpretive Criteria website, and remove claims for testing with *Acinetobacter* spp. and other non-Enterobacterales due to the lack of FDA-recognized breakpoints.

B Measurand:
Levofloxacin ≤0.125 - ≥8 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 Levofloxacin 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 Levofloxacin is a quantitative test.

Levofloxacin 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 cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens*.

Active *in vitro* but clinical significance unknown: *Citrobacter koseri, Citrobacter freundii, Enterobacter aerogenes, Klebsiella oxytoca, Morganella morganii, Pantoea agglomerans, Proteus vulgaris, Providentia rettgeri, Providencia stuartii.*

VITEK 2 AST-Gram Negative Levofloxacin also reports the susceptibility for the following additional organism as listed on the FDA Susceptibility Test Interpretive Criteria website: *Salmonella* 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.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

Limitation:

- The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing:
  Levofloxacin (lev02n): *Citrobacter freundii, E. aerogenes, E. cloacae, Klebsiella oxytoca, Morganella morganii, Pantoea agglomerans, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Salmonella* spp.

D Special Instrument Requirements:
VITEK 2 and VITEK 2 Compact Systems using VITEK 2 Systems 8.01 software (or later).

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.

The VITEK 2 AST-Gram Negative Levofloxacin has the following concentrations in the card: 0.25, 0.5, 2, 8 (equivalent standard method concentration by efficacy in µg/mL). The Levofloxacin MIC result range for the VITEK 2 is ≤0.125 to ≥8 µg/mL. For all species, the MIC result range indicates that the VITEK 2 system is capable of producing the following MIC results ≤0.125, 0.25, 0.5, 1, 2, 4 and ≥8 for AST-GN Levofloxacin test. This means the VITEK 2 systems does not provide results lower than 0.125µg/mL, or greater than 8 µg/mL for the AST-GN Levofloxacin 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 Levofloxacin (≤0.125 - ≥8)

B Predicate 510(k) Number(s):

K072038

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device **K222378**	Predicate **K072038**
Device Trade Name	VITEK 2 AST Gram Negative Levofloxacin (≤0.125 ≥8)	Same
General Device Characteristic Similarities		
Indications for Use	VITEK 2 AST Gram Negative Levofloxacin 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 Levofloxacin is a quantitative test. Levofloxacin 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 cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens*. Active *in vitro* but clinical significance unknown: *Citrobacter koseri, Citrobacter freundii, Enterobacter aerogenes, Klebsiella oxytoca, Morganella morganii, Pantoea agglomerans, Proteus vulgaris, Providentia rettgeri, Providencia stuartii.* 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.	VITEK Gram Negative Levofloxacin is designed for antimicrobial susceptibility testing of *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens, Citrobacter koseri, Citrobacter freundii, Enterobacter aerogenes, Klebsiella oxytoca, Morganella morganii, Pantoea agglomerans, Proteus vulgaris, Providencia rettgeri, Providencia stuartii*. VITEK 2 Gram Negative Levofloxacin is a quantitative test. It 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.
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	Same

Device & Predicate Device(s):	Device K222378	Predicate K072038
	organism	
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
Antimicrobial Agent	Levofloxacin	Same
Antimicrobial Concentrations	0.25, 0.5, 2, 4, 8 µg/mL	Same
Reporting Range	≤0.125 to ≥8 µg/mL	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
General Device Characteristic Differences		
Indicated Organisms	VITEK 2 AST-Gram Negative Levofloxacin also reports the susceptibility for the following additional organism as listed on FDA Susceptibility Test Interpretive Criteria Website: *Salmonella* spp.	*Acinetobacter baumannii, Acinetobacter lwoffi, Enterobacter sakazakii, Pseudomonas fluorescens*
Breakpoints	Enterobacterales: ≤0.5(S), 1(I), ≥2 (R) *P. aeruginosa*: ≤1(S), 2((I), ≤4 (R) *Salmonella* spp.: ≤0.125 (S), 0.25-1 (I), ≥2 (R)	Enterobacterales: ≤2(S), 4(I), 8(R) *P. aeruginosa*: ≤2(S), 4(I), 8(R) *Acinetobacter* spp.: ≤2(S), 4(I), 8(R)

VI Standards/Guidance Documents Referenced:

The CLSI Standards listed below were effective during the original clearance in K072038:

- CLSI M7 (M100-S16) "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard".

The CLSI Standards and FDA guidance document listed below were effective during the additional testing of *Salmonella* spp. and the re-analysis of Enterobacterales and *P. aeruginosa* in the current submission, K222378:

- CLSI M7-A7, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically" Seventh Edition (January 2006).
- CLSI M7, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically" Eleventh Edition (January 2018).
- CLSI M100, "Performance Standards for Antimicrobial Susceptibility testing"; 29th Edition (January 2019).
- Guidance for Industry and Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)

- Guidance on Informed Consent for in vitro Diagnostic Device Studies Using leftover Human Specimens that are Not Individually Identified; April 25, 2006.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility of the VITEK 2 AST-GN Levofloxacin was previously evaluated during review of K072038 and was determined to be acceptable (refer to the K072038 Decision Summary).

   In summary, a panel of 48 gram-negative isolates were tested in triplicate, each for three days at three sites using the manual and auto-dilution methods.

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):

   Quality Control (QC) testing, Inoculum and Growth failure for the VITEK 2 GN-AST Levofloxacin were previously evaluated during review of K072038 and were determined to be acceptable.

   QC specific to the change in breakpoints for Enterobacterales and *Pseudomonas aeruginosa* was not performed since the QC ranges used in K072038 were unchanged in the current submission and did not impact the performance.

   Additional quality control testing was performed during testing of *Salmonella* species as there are now FDA-recognized breakpoints for this organism group.

   The QC organisms recommended by both the FDA and CLSI, namely *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853, were tested a minimum of twenty times by both the VITEK 2 GN-AST Levofloxacin card and the reference method at one site. The Levofloxacin card (≤0.125 - ≥8 ug/mL) does not cover the expected result range of the QC organism *E. coli* ATCC 25922 of 0.008-0.06 ug/mL and produced off-scale QC MIC values. This was addressed in the labeling by adding the following footnote under the Quality Control Table:

"*Does not include the CLSI/FDA recommended dilution range for QC testing with this organism*".

Testing of off-scale *E. coli* ATCC 25922 was considered acceptable since testing of the secondary QC strain, *P. aeruginosa* ATCC 27853 produced on-scale MIC results. No QC trending was observed with *P. aeruginosa* ATCC 27853.

The quality control data generated during testing of *Salmonella* spp. was combined with that of the original clinical trial. The QC results obtained were in the recommended range >95% of the time for the reference method and with the VITEK 2 systems with all inoculation/reading methods as shown in **Table 1**, which is acceptable.

Table 1. Quality Control Result Frequencies for VITEK 2 (Auto-Dilution and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Organism	VITEK 2 Conc. µg/mL	BMD Conc. µg/mL	VITEK 2 Auto-Dilution	BMD	VITEK 2 Manual Dilution	BMD	VITEK 2 Compact Manual Dilution	BMD
E. coli (ATCC 25922) Expected Range: 0.008-0.06 µg/mL		≤0.0625		115		101		22
	≤0.125	0.125	115		101		22	
	0.25	0.25						
	0.5	0.5						
	1	1						
	2	2						
	4	4						
	≥8	8						
		16						
P. aeruginosa (ATCC 27853) Expected Range: 0.5-4 µg/mL		≤0.0625		1		1		
	≤0.125	0.125						
	0.25	0.25	1	1	1	1		
	0.5	0.5	1	11	3	11		1
	1	1	108	95	89	85	22	17
	2	2	8	7	9	24		4
	4	4						
	≥8	8						
		16						

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The VITEK 2 AST-GN Levofloxacin (≤0.125 - ≥8µg/mL) was originally cleared in premarket submission K072038 and included indications for Enterobacterales, *P. aeruginosa* and *Acinetobacter* spp. tested with VITEK 2 auto and manual dilution. The VITEK 2 Compact was not tested in the original submission. This was considered acceptable based on an equivalency study in K050002.

Since no changes were made to the design or dilution range of the VITEK 2 AST card, the performance of the VITEK 2 AST-GN Levofloxacin card with Enterobacterales and *P. aeruginosa* using revised interpretive criteria currently recognized by the FDA was evaluated using data obtained in the original 510(k) premarket submission K072038.

Since FDA no longer recognizes breakpoints for *Acinetobacter* spp. and other Non-Enterobacterales, 107 isolates of *Acinetobacter* spp. and 10 other Non-Enterobacterales were removed from the dataset.

The re-analyzed combined clinical and challenge data with the updated breakpoints included 346 Enterobacterales (295 clinical isolates and 51 challenge isolates) and 225 *P. aeruginosa* isolates (190 clinical isolates and 35 challenge isolates) that were originally tested on the VITEK 2 and the automated dilution, as shown in **Table 2**.

The re-analyzed challenge set of 51 Enterobacterales isolates and 35 *P. aeruginosa* isolates that were originally tested with the manual dilution method on the VITEK 2 instrument is shown in **Table 3**.

One *Salmonella* isolate was tested in the original submission K072038, and an additional 48 combined (17 clinical and 31 challenge) isolates of *Salmonella* spp. were tested and added to the original data set for evaluation with the VITEK 2 automatic dilution method to obtain the claim for this species. The challenge set of 31 *Salmonella* spp. isolates was also tested with the manual dilution method with the VITEK 2 and the VITEK 2 Compact Systems. The testing of *Salmonella* species was performed at one site with all dilution methods (manual and auto) and reading methods (VITEK 2 and VITEK 2 Compact). Data with *Salmonella* spp. is summarized in **Table 2** and **Table 3**.

Table 2. Re-analysis of the Original Performance for LEVOFLOXACIN with Enterobacterales, *P. aeruginosa* and Analysis of *Salmonella* spp. with the VITEK 2 (Auto Dilution)

VITEK 2 Systems	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Enterobacterales ≤S:0.5, I:1 , R: ≥2													
Clinical	295	294	99.66	23	22	95.65	288	97.63	66	223	7	0	0
Challenge	51	51	100	6	6	100	51	100	10	39	0	0	0
Combined	346	345	**99.71**	29	28	96.55	339	**97.98**	76	262	7	0	0
***Pseudomonas aeruginosa* ≤S:1, I:2, R: ≥4**													
Clinical	190	183	96.32	121	114	94.21	178	93.68	71	105	10	2	0
Challenge	35	35	100	31	31	100	32	91.43	5	22	3	0	0
Combined	225	218	**96.89**	152	145	95.39	210	**93.33**	76	127	13	2	0
***Salmonella* spp. ≤0.125, I: 025-1, R: ≥2**													
Clinical	17	17	100	1	1	100	17	100	1	15	0	0	0
Challenge	31	30	96.77	2	1	50	30	96.77	3	25	1	0	0
Combined	48	47	**97.92**	3	2	66.67	47	**97.92**	4	40	1	0	0

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
S – Susceptible isolates

min – minor errors
maj – major errors
vmj – very major errors

Essential Agreement (EA) occurs when there is agreement between the MIC result of the reference method and that of the 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 or those in which an off scale result is at least two doubling dilutions from the on scale result. 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 combined Essential Agreement (EA) and Categorical Agreement (CA) for each organism group (Enterobacterales, *P. aeruginosa* and *Salmonella* spp.) is >90% which is acceptable, as described in the "Class II Special Control Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 2009" (AST guidance). There were 7 minor errors (2.0%) with Enterobacterales, 13 minor errors (5.7%) and two major errors (1.6%) with *P. aeruginosa,* and one minor error (2.08%) with *Salmonella* spp.

Table 3. Re-analysis of the Original Performance with the Enterobacterales and *P. aeruginosa* Challenge Isolates and Analysis of *Salmonella* spp. on the VITEK 2 Systems (Manual Dilution)

	Tot	No.EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
***Enterobacterales*, ≤0.5(S), 1 (I), ≥2 (R)**													
VITEK 2	51	51	100	7	7	100	51	100	10	39	0	0	0
***Pseudomonas aeruginosa*, ≤1 (S), 2 (I), ≥4 (R)**													
VITEK 2	35	34	97.14	32	31	96.88	33	94.29	5	22	2	0	0
***Salmonella*, ≤0.125 (S), 0.25-1 (I), ≥2 (R)**													
VITEK 2	31	30	96.77	2	1	50	30	96.77	3	25	1	0	0
VITEK 2 Compact	31	30	96.77	2	1	50	30	96.77	3	25	1	0	0

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
S – Susceptible isolates

min – minor errors
maj – major errors
vmj – very major errors

Essential Agreement (EA) occurs when there is agreement between the MIC result of the reference method and that of the 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 or those in which an off scale result is at least two doubling dilutions from the on scale result. 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 EA and CA for each organism group (Enterobacterales, *P. aeruginosa* and *Salmonella* spp.) challenge set is >90% with the manual dilution option and the VITEK 2 systems, which is acceptable as noted in the AST guidance. There were 2 minor errors (5.71%) obtained with *P. aeruginosa*, one minor error with *Salmonella* spp. (3.22%) and no minor errors with Enterobacterales isolates. There were no major errors or very major errors obtained with any of the indicated organism tested when applying the current FDA-recognized breakpoints.

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included in the device labeling to address testing of non-indicated species:

> *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.*

Resistant Organisms

The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing:

- Levofloxacin (lev02n): *Citrobacter freundii, E. aerogenes, E. cloacae, Klebsiella oxytoca, Morganella morganii, Pantoea agglomerans, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Salmonella* spp.

MIC Trending Analysis

A trending reanalysis was performed using the combined (clinical and challenge) Enterobacterales and *P. aeruginosa* data obtained in K072038 to align with current trending analysis methods utilized and to also assess the data from additional testing with *Salmonella* spp. isolates with the VITEK 2 auto-dilution method.

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.

Organisms in which the difference between the percentage of isolates with higher vs. lower MIC values 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.

A statistically significant trend toward higher MIC values was observed *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and a statistically significant trend toward lower MIC values was observed *Serratia marcescens* species. No trending was observed with *Salmonella* spp. (**Table 4**). The following footnote to the performance table was included in the original package insert to address the trending observed for VITEK 2 AST-GN Levofloxacin:

> "*VITEK 2 Levofloxacin MIC values for Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa tended to be in exact agreement or at least one doubling dilution higher when compared to the reference agar dilution method. VITEK 2 Levofloxacin MIC values for Serratia marcescens tended to be in exact agreement or at least one doubling dilution lower when compared to the reference agar dilution*".

Table 4. Trending Analysis of VITEK 2 Gram Negative Levofloxacin.

Organism Group/Species	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
Citrobacter freundii	1	0, (0)	1	0, (0)	0% , (-79%, 79%)	No
Citrobacter koseri	0	0,0	0	0,0	0	NA
Enterobacter aerogenes	4	1, (25)	1	2, (50)	25% , (-32%, 66%)	No
Enterobacter cloacae	3	1, (33.33)	1	1, (33.33)	0% , (-53%, 53%)	No
Escherichia coli	8	1, (12.5)	1	6, (75)	62% , (14%, 83%)	**Yes**
Hafnia alvei	0	0,0	0	0,0	0	NA
Klebsiella oxytoca	0	0,0	0	0,0	0	NA
Klebsiella pneumoniae	1	0, (0)	0	1, (100)	100% , (-12%, 100%)	**Yes***
Klebsiella pneumoniae ssp pneumoniae	7	0, (0)	0	7, (100)	100% , (50%, 100%)	**Yes**
Morganella morganii	1	0, (0)	0	1, (100)	100% , (-12%, 100%)	**Yes***
Pantoea agglomerans	1	0, (0)	1	0, (0)	0% , (-79%, 79%)	No
Proteus mirabilis	4	0, (0)	3	1, (25)	25% , (-28%, 70%)	No
Proteus vulgaris	0	0,0	0	0,0	0	NA
Providencia rettgeri	2	0, (0)	2	0, (0)	0% , (-66%, 66%)	No
Providencia stuartii	1	0, (0)	1	0, (0)	0% , (-79%, 79%)	No
Enterobacterales	41	8, (19.51)	14	19, (46.34)	27% , (6%, 44%)	No
P. aeruginosa	157	9, (5.73)	91	57, (36.31)	31% , (22%, 39%)	**Yes**
Salmonella enterica ssp *enterica*	0	0,0	0	0,0	0	NA
Salmonella group	0	0,0	0	0,0	0	NA
Salmonella ser. *enteritidis*	0	0,0	0	0,0	0	NA
Salmonella spp.	1	0, (0)	1	0, (0)	0% , (-79%, 79%)	No
Serratia liquefaciens	0	0,0	0	0,0	0	NA
Serratia marcescens	8	5, (62.5)	3	0, (0)	-62% , (-86%, -17%)	**Yes**

*Not statistically significant

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:

The FDA and CLSI susceptibility interpretive criteria for Levofloxacin are as listed in **Table 5**.

Table 5. FDA-Recognized Interpretive Criteria for Levofloxacin

	Minimum Inhibitory Concentrations (µg/mL)[a]		
Organisms	**S**	**I**	**R**
Enterobacterales	≤0.5	1	≥2
Salmonella spp.	≤0.12	0.25-1	≥2
Pseudomonas aeruginosa	≤1	2	≥4

S = Susceptible; I = Intermediate; R = Resistant

[a]According to CLSI M100-Ed33 and FDA STIC Website https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

VIII Proposed Labeling:

The labeling was updated to include:

- The statement required by the 21st Century Cures Act legislation to address testing of non-indicated species.
- Updated breakpoints for Enterobacterales and *P. aeruginosa* with Levofloxacin.
- Updated performance using the current FDA-recognized breakpoints, along with a limitation for lack of insufficient resistant isolates to reflect results obtained from this evaluation.
- Inclusion of *Salmonella* spp. in the Intended Use/Indication for use along with supportive performance data using currently recognized breakpoints.
- Removal of claims for testing of *Acinetobacter* spp. and other Non-Enterobacterales due to lack of FDA-recognized breakpoints.

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 System with Levofloxacin when revised breakpoints for this drug 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 Levofloxacin 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.