510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193358

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

MicroScan Dried Gram-Negative MIC/Combo Panels with Levofloxacin (Lvx) (0.008 -16 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LTT	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
JWY	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology
LRG	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 obtain a substantial equivalence determination for levofloxacin at concentrations of 0.008 – 16 µg/mL with the MicroScan Dried Gram-Negative MIC/Combo Panels for susceptibility testing of non-fastidious Gram-negative organisms.

B Measurand:

Levofloxacin in the dilution range of 0.008 – 16 μg/mL

C Type of Test:

Quantitative antimicrobial susceptibility test (AST)

III Intended Use/Indications for Use:

A Intended Use(s):
MicroScan Dried Gram-Negative MIC/Combo Panels are designed for use in determining quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative gram-negative bacilli.

B Indication(s) for Use:
The MicroScan Dried Gram-Negative MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram-negative bacilli. After inoculation, panels are incubated for 16 - 20 hours at 35°C +/- 1°C in a non-CO_2 incubator, and read either visually or with MicroScan instrumentation, according to the Package Insert.

This particular submission is for updated susceptibility test interpretative criteria for Enterobacteriaceae and Pseudomonas aeruginosa for the antimicrobial levofloxacin (Lvx) at concentrations of 0.008 to 16 μg/mL to the test panel.

Levofloxacin has been shown to be active in vitro against most strains of microorganisms listed below, as described in the

FDA-approved package insert for this antimicrobial agent.

Active *In Vitro* and in Clinical Infections Against:

Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Active *In Vitro* but clinical significance is unknown:

Citrobacter koseri
Citrobacter freundii
Enterobacter aerogenes
Klebsiella oxytoca
Morganella morganii
Pantoea agglomerans

Proteus vulgaris
Providencia rettgeri
Providencia stuartii

The MicroScan Dried Gram-Negative MIC/Combo Panel also reports the susceptibility for the following additional organisms as listed on the FDA Susceptibility Test Interpretative Criteria web site:

Salmonella spp.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The ability of the MicroScan Dried Gram-Negative Panels to detect resistance to levofloxacin is unknown for the following species because an insufficient number of resistant strains were available at the time of comparative testing: C. koseri, P. vulgaris, and P. agglomerans. Isolates yielding MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory.

Due to the occurrence of very major errors with levofloxacin and the autoSCAN-4 with both turbidity and Prompt inoculation methods, isolates of P. aeruginosa that provide and MIC of 1 µg/mL should be interpreted manually prior to reporting.

D Special Instrument Requirements:

MicroScan panels can be read either manually or automatically on the WalkAway or autoSCAN-4 instrument systems.

IV Device/System Characteristics:

A Device Description:

The MicroScan Dried Gram-Negative MIC/Combo panel with levofloxacin is used to determine the quantitative and/or qualitative antimicrobial agent susceptibility of aerobic and facultatively anaerobic gram-negative bacilli colonies grown on solid media. After inoculation, panels are incubated for 16-20 hours at 35°C ± 1° in a non-CO_2 incubator and read either visually or with MicroScan instrumentation according to the package insert.

Inoculation methods: Turbidity or Prompt Inoculation System

Read methods: Manual, MicroScan WalkAway System and MicroScan autoSCAN-4

B Principle of Operation:

The antimicrobial susceptibility tests are dehydrated miniaturizations of the broth dilution susceptibility test. Various antimicrobial agents are diluted in Mueller Hinton broth supplemented with calcium and magnesium to concentrations spanning the range of clinical

interest. Breakpoint Combo panels use concentrations equivalent to the categorical breakpoints identified/recognized by FDA. After inoculation and rehydration with a standardized suspension of organism and incubation at 35°C for a minimum of 16 hours, the minimum inhibitory concentration (MIC) for the test organism is determined by observing the lowest antimicrobial concentration showing inhibition of growth.

V Substantial Equivalence Information:

A Predicate Device Name(s):

MicroScan Dried Gram Negative MIC/Combo Panels with Meropenem (Mer) (0.004-32ug/mL)

B Predicate 510(k) Number(s):

K192355

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device: K193358**	**Predicate: K192355**
Device Trade Name	MicroScan Dried Gram Negative MIC/Combo Panels - Levofloxacin	MicroScan Dried Gram Negative MIC/Combo Panels - Meropenem
General Device Characteristic Similarities		
Intended Use/Indications For Use	Determination of susceptibility with gram-negative bacilli	Same
Technology	Overnight microdilution MIC susceptibility test	Same
Specimen	Isolated colonies from culture	Same
Incubation Temperature	35 ℃ ± 1℃	Same
Incubation Atmosphere	Aerobic	Same
Incubation Time	16 – 20 hours	Same
Reading Method	Automated (WalkAway or autoSCAN-4) or Manual	Same
Result Reported	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Same

General Device Characteristic Differences		
Antimicrobial Agent	Dried Levofloxacin 0.008 – 16 µg/mL	Dried Meropenem 0.004 – 32 µg/mL

VI Standards/Guidance Documents Referenced:

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA. August 2009
2. CLSI M07-A10. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 10th ed. (January 2015)
3. CLSI M100. Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. (January 2019)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study was conducted at three external sites using 15 isolates of gram-negative bacilli that were consistent with the intended use. The range of levofloxacin dilutions tested was 0.008 - 16 µg/mL. Isolates were tested in triplicate over three days for a total of 405 data points (27 data points per isolate). The isolates tested in the reproducibility study included: *C. freundii* complex (1 isolate), *E. cloacae* (1 isolates), *E. coli* (4 isolates), *K. oxytoca* (2 isolates), *K. pneumoniae* (3 isolates), *P. aeruginosa* (1 isolate), *P. mirabilis* (1 isolate), *S. marcescens* (1 isolate), and *S. typhi* (1 isolate).

Inocula were prepared using both the turbidity and Prompt methods and results were read manually (visually) and with the WalkAway and autoSCAN-4 instrument systems. The majority of data points were on-scale and the majority were within ± one doubling dilution of the mode MIC (Table 2). For those read/inoculation combinations that included off-scale results, reproducibility was assessed as worst-case in addition to best-case.

The reproducibility results are acceptable.

Table 2. Reproducibility of Levofloxacin with all Inoculation and Read Methods

Read Method	Reproducibility No. within ± dilution of the mode MIC value (%)			
	Prompt Inoculation		Turbidity Inoculation	
	Best	Worst	Best	Worst
WalkAway	402/405 (99.3)	N/A*	401/405 (99.0)	399/405 (98.5)
autoSCAN-4	403/405 (99.5)	N/A*	403/405 (99.5)	402/405 (99.3)
Manual	402/405 (99.3)	397/405 (98.0)	402/405 (99.3)	396/405 (97.8)

*All results were on-scale.

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):

   Inoculum Density Check. A spectrophotometric device, the MicroScan Turbidity Meter, was used to ensure the accuracy of the turbidity inoculation method. A zero check of the turbidity meter was performed daily. The inocula prepared using the turbidity method were standardized using a reading of 0.08 ± 0.02 (equivalent to a 0.5 McFarland barium sulfate turbidity standard). The digital reading was recorded for each isolate and was considered acceptable based on recommendations in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems*.

   Inoculum density data for the Prompt inoculation system was collected from suspensions of the QC strain *E. coli* ATCC 25922 and for all reproducibility isolates. Average colony counts were within the acceptable range for the QC strain and for all reproducibility isolates.

   Purity Check. Purity checks were performed on all isolates for each inoculum preparation; only results from pure cultures were included.

   Growth Failure Rate. Less than 10% of isolates demonstrated no growth on the dried test panel.

   Quality Control Testing. The CLSI-recommended QC organisms *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested with all inoculation and read methods using 12 dilutions of levofloxacin (0.008 – 16 µg/mL). The reference panel was inoculated using the turbidity method only. For both QC strains, quality control results were within the acceptable range for all inoculation and read methods. Results of current QC testing are shown in Table 3 below and demonstrate that QC results obtained were in the recommended range >95% of the time for the reference method and with all inoculation/reading methods for this device.

   Table 3. Quality Control Results for all Inoculation and Read Methods for Levofloxacin

Organism	Conc. (µg/mL)	Reference*	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4**	Manual	WalkAway	AS4**
E. coli ATCC 25922 Expected Range:	≤0.008	-	-	-	-	-	-	-
	0.015	82	164	167	175	178	176	181
	0.03	107	24	18	12	9	11	5
	0.06	-	-	-	-	2	2	2
	0.12	-	-	-	-	-	-	-
	0.25	-	1	1	1	-	-	-

0.008-0.006 µg/mL								
P. aeruginosa ATCC 27853 Expected Range: 0.5-4 µg/mL	0.25	-	-	-	-	-	-	-
	0.5	1	25	3	33	149	113	155
	1	177	161	175	153	40	76	32
	2	11	3	6	3	-	-	-
	4	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-
	16	-	-	-	-	-	-	-
	>16	-	-	1	-	-	-	-

*Reference panel was inoculated using the turbidity method and interpreted manually.
**autoSCAN-4

6. Detection Limit:

   Not Applicable

7. Assay Cut-Off:

   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

   The results obtained with the MicroScan Dried Gram-Negative MIC/Combo Panel with levofloxacin (dilution range 0.008 – 16 µg/mL) were compared to results obtained using a frozen broth microdilution reference panel (dilution range 0.008 – 16 µg/mL). Clinical isolates were evaluated at three testing sites in the U.S in a single study; challenge isolates were evaluated in one separate study performed at one external site.

   The reference panel was prepared as described in CLSI document M07-A10 except for the use of Pluronic-F in the inoculum water for the reference panel. A summary of historical data from eight previously cleared antimicrobial tests to include ciprofloxacin was provided in the submission which demonstrated that including the wetting agent did not affect testing. In addition, the QC testing that was conducted during the clinical study was acceptable.

   For the reference method and MicroScan panels inoculated using the turbidity method, panels were inoculated using the same standardized suspension further diluted into 25 mL of water with Pluronic-D (for the MicroScan dried panels) or Pluronic-F (for the frozen reference panels). MicroScan panels were also inoculated using the Prompt inoculation method with isolates inoculated into the Prompt inoculation bottle. Reference panels were read manually (visually); MicroScan panels inoculated with both inoculation methods were read using the WalkAway and autoSCAN-4 instruments and by manual read.

   Clinical Study
   To determine the performance of the MicroScan Dried Gram-Negative MIC/Combo Panel with Levofloxacin, a total of 541 *Enterobacteriaceae*, 19 *Salmonella* spp., and 79 *P. aeruginosa* clinical isolates were evaluated separately based on unique susceptibility test

interpretive criteria with all inoculation and read methods (Tables 4 and 5). The testing included the following indicated *Enterobacteriaceae* species: *C. freundii* (12 isolates), *C. koseri* (49 isolates), *K. (Enterobacter) aerogenes* (32 isolates), *E. cloacae* (48 isolates), *E. coli* (77 isolates), *K. oxytoca* (47 isolates), *K. pneumoniae* (89 isolates), *M. morganii* (41 isolates), *P. agglomerans* (1 isolate), *P. mirabilis* (56 isolates), *P. vulgaris* (17 isolates), *P. rettgeri* (19 isolates), *P. stuartii* (21 isolates), *S. marcescens* (32 isolates), and *Salmonella* spp. (13 non-speciated isolates), and *S. enteritidis* (6 isolates). An additional 63 isolates of non-indicated *Enterobacteriaceae* species (10% of the total number of isolates tested) were also tested and included in the evaluation. Of all the clinical isolates tested, 462 (65.9%) were fresh (collected and tested within seven days), 218 (31.0%) were recent (isolated and tested within six months), and 22 (3.1%) were stock (isolated and tested after six months of isolation).

Challenge Study
A total of 123 *Enterobacteriaceae* challenge isolates were evaluated. These included: *C. koseri* (3 isolates), *K. aerogenes* (2 isolates), *E. cloacae* (8 isolates), *E. coli* (12 isolates), *K. oxytoca* (6 isolates), *K. pneumoniae* (10 isolates), *M. morganii* (1 isolate), *P. mirabilis* (7 isolates), *P. rettgeri* (1 isolate), *S. marcescens* (4 isolates), and *S. typhi* (64 isolates). In addition, the following non-indicated species were evaluated; *C. freundii* complex (2 isolates), and *S. liquefaciens* (3 isolates). A total of 14 challenge isolates of *P. aeruginosa* were evaluated.

Results for EA, CA and categorical errors for *Enterobacteriaceae* and *P. aeruginosa* for all inoculation and read methods are shown in Tables 4 and 5 below. Essential agreement of evaluable results was calculated considering MIC results that were clearly identical to reference method results or clearly ≥ one doubling dilution higher or lower than the reference method results. Overall results for *Enterobacteriaceae* and for *P. aeruginosa* with all inoculation and read methods were acceptable.

For *C. koseri, P. vulgaris*, and *P. agglomerans*, no resistant isolates were available for evaluation during clinical or challenge testing. The sponsor included the following limitation in the device labeling:

> *The ability of the MicroScan Dried Gram-Negative Panels to detect resistance to levofloxacin is unknown for the following species because an insufficient number of resistant strains were available at the time of comparative testing: C. koseri, P. vulgaris, and P. agglomerans. Isolates yielding MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory.*

The overall EA and CA performance for *Enterobacteriaceae* for the WalkAway, autoSCAN-4, and manual read methods were acceptable for each inoculation method (Tables 4 and 5). Testing using the autoSCAN-4 for both inoculation method resulted in two additional very major errors for *P. mirabilis* and *S. marcescens*. However, this was considered acceptable given that there was only one VME each and a limited number of resistant isolates for these species. In addition, the sponsor included the following footnote to the performance table in the device labeling:

> *One resistant strain of Proteus mirabilis and Serratia marcescens had a single very major error compared to the reference method when using the autoSCAN-4 instrument*

with both turbidity and Prompt inoculation methods.

In addition, one very major error was observed for *K. pneumoniae* for all read and inoculation methods resulting in a VME rate of 5.3% (1/19) for this species. As a result, the sponsor included results from their Assay Development-3 Project which consisted of 24 additional levofloxacin resistant *K. pneumoniae* strains. Inclusion of these isolates resulted in an overall VME rate of 2.3% (1/43). Given this, the sponsor was not requested to test additional isolates. The sponsor included the following footnote in the device labeling:

One resistant Klebsiella pneumoniae strain resulted in a very major error when compared to the reference method across all read and inoculation methods.

Salmonella spp. results were evaluated separately from *Enterobacteriaceae* due to differences in susceptibility test interpretive criteria. In addition to the 21 isolates that were tested in this clinical study, the sponsor included results obtained with an additional 62 *S. typhi* challenge isolates for a total of 83 *Salmonella* spp. isolates. The overall EA and CA performance for this organism were acceptable for each read method and inoculation method (Tables 4 and 5) and there were no major or very major errors.

The overall EA and CA performance for *P. aeruginosa* was acceptable for all read and inoculation methods. Testing for *P. aeruginosa* yielded one VME for the WalkAway and Prompt read/inoculation combination (1/34, 2.9%), four VMEs with the autoSCAN-4 and Prompt (4/34, 11.8%), two VMEs with the autoSCAN-4 and turbidity inoculation (2/34, 5.9%), and one VME when read manually with turbidity inoculation. Due to the high VME rates, as a separate analysis, the sponsor included results from their Assay Development-3 Project which consisted of 18 levofloxacin resistant *P. aeruginosa* strains for the WalkAway/Prompt comparison and 21 resistant strains for the manual/turbidity comparison. All results were acceptable yielding a 1.9% (1/52) VME for the WalkAway/Prompt, and 1.8% (1/55) VME rate for the manual/turbidity combinations, however, this is not reflected in performance tables 4 and 5 below. Given that there was only one very major error for the WalkAway and manual methods and acceptable VME rates with the pooled data, the performance was considered acceptable. However, due to the high VME rate for the autoSCAN-4, the sponsor included the following as a limitation should the user yield an MIC result of 1 µg/mL:

Due to the occurrence of very major errors with levofloxacin and the autoSCAN-4 with both turbidity and Prompt inoculation methods, isolates of P. aeruginosa that provide and MIC of 1 µg/mL should be interpreted manually prior to reporting.

For this review, the interpretative criteria are applied to *Enterobacteriaceae, Salmonella* spp., and *Pseudomonas aeruginosa* according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and Cosmetic Act, the following statements were included under Warning and Precautions Section in the MicroScan Dried Gram-Negative MIC/Combo Panels package insert:

The safety and efficacy of antimicrobial agents tested by this 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 section in the drug label. The clinical significance in those instances is unknown. The

approved labeling for specific antimicrobial agents provides the uses for which the antimicrobial drug is approved.

Table 4. Performance of MicroScan Dried Gram-Negative Panels with Levofloxacin, Using Prompt Inoculation and All Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
WalkAway Read													
***Enterobacteriaceae**, ≤0.5 (S), 1 (I), ≥2 (R)**													
Clinical	604	580	96.0	575	551	95.8	586	97.0	105	486	17	0	1
Challenge	59	56	94.9	54	51	94.4	55	93.2	28	29	3	0	1
Total	663	636	95.9	629	602	95.7	641	96.7	133	515	20	0	2
***Salmonella* spp., ≤0.12 (S), 0.25-1 (I), ≥2 (R)**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	64	64	100	64	64	100	63	98.4	19	21	1	0	0
Total	83	83	100	83	83	100	82	98.8	19	38	1	0	0
***P. aeruginosa*, ≤1 (S), 2 (I), ≥4**													
Clinical	79	74	93.7	70	65	92.9	73	92.4	24	51	4	1	1
Challenge	14	13	92.9	13	12	92.3	12	85.7	10	3	2	0	0
Total	93	87	93.6	83	77	92.8	85	91.4	34	54	6	1	1
autoSCAN-4 Read													
***Enterobacteriaceae**, ≤0.5 (S), 1 (I), ≥2 (R)**													
Clinical	604	570	94.4	576	542	94.1	585	96.9	105	486	17	0	2
Challenge	59	54	91.5	54	49	90.7	54	91.5	28	29	2	0	2
Total	663	624	94.1	630	591	93.8	639	96.4	133	515	19	1	4
***Salmonella* spp., ≤0.12 (S), 0.25-1 (I), ≥2 (R)**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	64	64	100	64	64	100	63	98.4	19	21	1	0	0
Total	83	83	100	83	83	100	82	98.8	19	38	1	0	0
***P. aeruginosa*, ≤1 (S), 2 (I), ≥4**													
Clinical	79	72	91.1	70	63	90.0	71	89.9	24	51	4	1	3
Challenge	14	13	92.9	13	12	92.3	12	85.7	10	3	1	0	1
Total	93	85	91.4	83	75	90.4	83	89.3	34	54	5	1	4
Manual Read													
***Enterobacteriaceae**, ≤0.5 (S), 1 (I), ≥2 (R)**													
Clinical	604	582	96.4	574	552	96.2	586	97.0	105	486	17	0	1
Challenge	59	56	94.9	54	51	94.4	55	93.2	28	29	3	0	1
Total	663	638	96.2	628	603	96.0	641	96.7	133	515	20	0	2
***Salmonella* spp., ≤0.12 (S), 0.25-1 (I), ≥2 (R)**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	64	64	100	64	64	100	63	98.4	19	21	1	0	0
Total	83	83	100	83	83	100	82	98.8	19	38	1	0	0
***P. aeruginosa*, ≤1 (S), 2 (I), ≥4**													
Clinical	79	75	94.9	70	66	94.3	75	94.9	24	51	3	1	0
Challenge	14	13	92.9	13	12	92.3	12	85.7	10	3	2	0	0
Total	93	88	94.6	83	78	94.0	87	93.6	34	54	5	1	0

*Includes non-indicated species (68/663, 10.3%).

EA – Essential Agreement (± 1 dilution)
CA – Category Agreement
EVAL – Evaluable isolates
No. R/S – Resistant/Susceptible
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the MicroScan Dried Gram-Negative MIC/Combo Panel 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 MicroScan Dried Gram-Negative MIC/Combo Panel. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by the MicroScan Dried Gram-Negative MIC/Combo Panel.

Table 5. Performance of MicroScan Dried Gram-Negative Panels with Levofloxacin, Using Turbidity Inoculation and All Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
WalkAway Read													
***Enterobacteriaceae**, ≤0.5 (S), 1 (I), ≥2 (R)**													
Clinical	604	590	97.7	576	562	97.6	591	97.9	105	486	12	0	1
Challenge	59	56	94.9	55	52	94.6	54	91.5	28	29	4	0	1
Total	663	646	97.4	631	614	97.3	645	97.3	133	515	16	0	2
***Salmonella* spp., ≤0.12 (S), 0.25-1 (I), ≥2 (R)**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	64	64	100	64	64	100	64	100	19	21	0	0	0
Total	83	83	100	83	83	100	83	100	19	38	0	0	0
***P. aeruginosa*, ≤1 (S), 2 (I), ≥4**													
Clinical	79	77	97.5	70	68	97.1	75	94.9	24	51	4	0	0
Challenge	14	14	100	13	13	100	13	92.9	10	3	1	0	0
Total	93	91	97.9	83	81	97.6	88	94.6	34	54	5	0	0
autoSCAN-4 Read													
***Enterobacteriaceae**, ≤0.5 (S), 1 (I), ≥2 (R)**													
Clinical	604	580	96.0	576	552	95.8	589	97.5	105	486	13	0	2
Challenge	59	55	93.2	55	51	92.7	54	91.5	28	29	3	0	2
Total	663	635	95.8	631	603	95.6	643	97.0	133	515	16	0	4
***Salmonella* spp., ≤0.12 (S), 0.25-1 (I), ≥2 (R)**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	64	64	100	64	64	100	63	98.4	19	21	1	0	0
Total	83	83	100	83	83	100	82	98.8	19	38	1	0	0
***P. aeruginosa*, ≤1 (S), 2 (I), ≥4**													
Clinical	79	74	93.7	70	65	92.9	72	91.1	24	51	5	0	2
Challenge	14	12	85.7	14	12	85.7	12	85.7	10	3	2	0	0
Total	93	86	92.5	84	77	91.2	84	90.3	34	54	7	0	2
Manual Read													
***Enterobacteriaceae**, ≤0.5 (S), 1 (I), ≥2 (R)**													
Clinical	604	589	97.5	576	561	97.4	591	97.9	105	486	12	0	1
Challenge	59	56	94.9	55	52	94.6	54	91.5	28	29	4	0	1
Total	663	645	97.3	631	613	97.1	645	97.3	133	515	16	0	2
***Salmonella* spp., ≤0.12 (S), 0.25-1 (I), ≥2 (R)**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	64	64	100	64	64	100	61	95.3	19	21	3	0	0
Total	83	83	100	83	83	100	80	96.4	19	38	3	0	0
***P. aeruginosa*, ≤1 (S), 2 (I), ≥4**													
Clinical	79	76	96.2	70	67	95.7	76	96.2	24	51	2	0	1
Challenge	14	13	92.9	14	13	92.9	13	92.9	10	3	1	0	0
Total	93	89	95.7	84	80	95.2	89	95.7	34	54	3	0	1

*Includes non-indicated species.

Resistance Mechanism Characterization

Challenge isolates of *Enterobacteriaceae* and *P. aeruginosa* harboring various molecular mechanisms of resistance noted in the FDA approved drug label were tested with levofloxacin.

Isolates from the following CDC and FDA Antibiotic Resistance Isolate Bank panels were evaluated: *Enterobacteriaceae* Carbapenem Breakpoint Panel, *Enterobacteriaceae* Carbapenemase Diversity Panel, Gram Negative Carbapenemase Detection Panel, and the Ceftolozane/tazobactam Panel.

Trending

An analysis of trending was conducted using the combined clinical and challenge data for each organism group and for each inoculation and read method. This trending calculation takes into account MIC values that are determined to be one or more doubling dilution lower or higher compared to 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.

Trending results for indicated species were evaluated to determine if species-specific trends were observed. Species or 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 provides higher or lower MIC values compared to the reference is addressed in labeling.

A trend toward lower MIC readings was observed for *Enterobacteriaceae* using all read and inoculation methods (Table 6) in comparison to the reference method. In addition, a trend toward lower MIC readings was observed for *P. aeruginosa* using all read methods and turbidity inoculation method and autoSCAN-4 reading method using the Prompt inoculation method. Given this, the sponsor included the following footnote to the performance table in the device labeling:

> *An MIC bias for Levofloxacin and Enterobacteriaceae with all read/inoculation methods, and Pseudomonas aeruginosa with all read methods/turbidity inoculation and the autoSCAN-4/Prompt inoculation tended to be one doubling dilution lower than the reference method.*

Table 6: Trending for Enterobacteriaceae and P. aeruginosa For All Read/Inoculation Methods

Inoculation/ Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
Prompt/ WalkAway	*Enterobacteriaceae**	719	293 (40.8)	399 (55.5)	27 (3.8)	-37.0	Yes
	P. aeruginosa	84	20 (23.8)	56 (66.7)	8 (9.5)	-14.3	No
Prompt/ autoSCAN-4	*Enterobacteriaceae**	721	346 (48.0)	350 (48.6)	25 (3.5)	-44.5	Yes
	P. aeruginosa	85	32 (37.7)	48 (56.5)	5 (5.9)	-31.8	Yes
Prompt/ Manual	*Enterobacteriaceae**	718	292 (40.7)	395 (55.0)	31 (4.3)	-36.4	Yes
	P. aeruginosa	84	22 (26.2)	53 (63.1)	9 (10.7)	-15.5	No
Turbidity/ WalkAway	*Enterobacteriaceae**	721	326 (45.2)	376 (52.2)	19 (2.6)	-42.6	Yes
	P. aeruginosa	85	36 (42.4)	44 (51.8)	5 (5.9)	-36.5	Yes
Turbidity/ autoSCAN-	*Enterobacteriaceae**	722	395 (54.7)	310 (42.9)	17 (2.4)	-54.7	Yes

Inoculation/ Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
4	*P. aeruginosa*	85	47 (55.3)	34 (40)	4 (4.7)	-50.6	Yes
Turbidity/ Manual	*Enterobacteriaceae**	721	335 (46.5)	366 (50.8)	20 (2.8)	-43.7	Yes
	P. aeruginosa	85	37 (43.5)	43 (50.6)	5 (5.9)	-37.7	Yes

*Includes *Salmonella* spp. and non-indicated species.

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 7. FDA-Recognized Interpretive Criteria for Levofloxacin

Organism	Interpretive Criteria for Levofloxacin (µg/mL)[a]		
	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≤ 0.5	1	≥ 2
P. aeruginosa	≤ 1	2	≥ 4
Salmonella spp.	≤ 0.12	0.25 - 1	≥ 2

[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 Beckman Coulter intends to use to evaluate the MicroScan Dried Gram-Negative MIC/Combo Panels with Levofloxacin (Lvx) (0.008 - 16 µg/mL) when revised breakpoints for levofloxacin are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Beckman Coulter 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.