510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193536

B Applicant

Beckman Coulter, Inc

C Proprietary and Established Names

MicroScan Dried Gram Negative MIC/Combo Panels with Ciprofloxacin (Cp) (0.004 - 8 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LTT, JWY, LRG, 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 ciprofloxacin at concentrations of 0.004 – 8 µg/mL with the MicroScan Dried Gram-Negative MIC/Combo Panels for susceptibility testing of non-fastidious gram negative organisms.

B Measurand:

Ciprofloxacin in the dilution range of 0.004 – 8 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 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 degrees C +/- 1 degree centigrade 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 interpretive criteria for *Enterobacteriaceae* and *Pseudomonas aeruginosa,* as well as expanding *Salmonella* ser. Typhi interpretive criteria to all *Salmonella* spp. for the antimicrobial ciprofloxacin (Cp) at concentrations of 0.004 to 8 ug/mL to the test panel.

Ciprofloxacin 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:

Citrobacter koseri
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella ser. Typhi
Serratia marcescens
Shigella flexneri
Shigella sonnei

Active *in vitro* but clinical significance is unknown:

Enterobacter aerogenes
Klebsiella oxytoca
Salmonella enteritidis

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 ciprofloxacin 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, Shigella sonnei and Salmonella enteritidis. Isolates yielding MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory.

Results obtained with ciprofloxacin and E. cloacae with all read methods/Prompt, E. aerogenes with WalkAway/Prompt and manual/Prompt, S. sonnei with manual/Prompt and S. marcescens with the autoSCAN-4/Prompt and manual/Prompt have shown discrepant MICs when compared with the reference method. If critical to patient care, isolates of those species should be retested using the turbidity inoculation method. In addition, discrepant MICs were observed with ciprofloxacin and C. koseri with turbidity/manual read; if critical to patient care, isolates of C. koseri should be tested with an alternate inoculation/read method.

Due to low categorical agreement and increased occurrence of very major errors for P. aeruginosa and ciprofloxacin with the autoSCAN-4 and Prompt inoculation, results should be confirmed by manual read 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 ciprofloxacin 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 determined or 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) (0.004-32µg/mL)

B Predicate 510(k) Number(s):
K192355

C Comparison with Predicate(s):

Table 1. Comparison with Predicate

Device & Predicate Device(s):	**Device: K193536**	**Predicate: K192355**
Device Trade Name	MicroScan Dried Gram Negative MIC/Combo Panels - Ciprofloxacin	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 °C ± 1°C	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 Ciprofloxacin 0.004 – 8 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
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 12 isolates of gram-negative bacilli that were consistent with the intended use. The range of ciprofloxacin dilutions tested was 0.004-8 µg/mL. Isolates were tested in triplicate over three days for a total of 324 data points (27 data points per isolate). The isolates tested in the reproducibility study included: *C. freundii* complex (1 isolate), *C. koseri* (1 isolate), *E. cloacae* (1 isolate), *E. coli* (2 isolates), *K. oxytoca* (2 isolates), *K. pneumoniae* (2 isolates), *S. marcescens* (1 isolate), *Salmonella* ser. Typhi (1 isolate) and *P. aeruginosa* (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 within ± one doubling dilution of the mode MIC value. The data was analyzed as described in the Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems. Because results from all sites were all on-scale, only a single combined reproducibility result is reported for each read method.

The reproducibility results are acceptable and are shown in Table 2 below.

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

Read Method	Reproducibility No. within ±dilution of the mode MIC value (%)	
	Prompt Inoculation	**Turbidity Inoculation**
WalkAway	318/324 (98.1)	323/324 (99.7)
autoSCAN-4	315/324 (97.2)	319/324 (98.5)
Manual	318/324 (98.1)	322/324 (99.4)

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 colony counts were evaluated from suspensions of the QC strain *E. coli* ATCC 25922 and were found to be within the acceptable concentration range as recommended in the CLSI document M07, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically.*

   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. The overall average colony count was within the acceptable range for all isolates.

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

   Growth Failure Rate. All organisms evaluated showed growth on the dried test panels.

   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 ciprofloxacin (0.004 – 8 µg/mL). The reference panel was inoculated using the turbidity method only. In this submission the QC range for both *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 reflect the current MIC ranges recommended in the CLSI document M100, *Performance Standards for Antimicrobial Susceptibility Testing* 29th ed. 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 acceptable QC results can be obtained with this device for >95% of tests.

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

Organism	Conc. (µg/mL)	Reference	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
E. coli ATCC 25922 Expected Range 0.004-0.016 µg/mL	≤0.004	2						
	0.008	175	66	40	149	40	13	131
	0.016	12	122	144	38	148	175	57
	0.03			1				
	0.06					1	1	
	0.12							
	0.25		1	1	1			
	0.5							
	1							
	2							
	4							
	8							
P. aeruginosa ATCC 27853 Expected Range 0.12 – 1.0 µg/mL	≤0.004							
	0.008							
	0.016							
	0.03							
	0.06							
	0.12							
	0.25	131	63	41	123	171	175	183
	0.5	58	124	141	66	18	14	4
	1		2	3				
	2							
	4							
	8							

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 ciprofloxacin (dilution range 0.004 – 8 µg/mL) were compared to results obtained using a frozen broth microdilution reference panel (dilution range 0.004 – 8 µg/mL). Clinical isolates were evaluated at three testing sites in the U.S. in a single study; challenge isolates were evaluated in two separate studies performed at internal and external sites.

   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 validation study was

performed to demonstrate the equivalence between reference panels inoculated with organisms suspended in water supplemented with Pluronic-F and reference panels inoculated with autoclaved deionized water without Pluronic-F as part of studies performed for K172912, MicroScan Dried Gram-Negative MIC/Combo Panels with Ciprofloxacin-S (0.004-8 µg/mL).The effect of Pluronic-F in the reference panel was determined with 11 *Salmonella* ser.Typhi isolates; performance was determined to be 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 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 Isolates

To determine the performance of the MicroScan Dried Gram-Negative MIC/Combo Panel with Ciprofloxacin, a total of 604 non-*Salmonella Enterobacteriaceae* clinical isolates were evaluated with all inoculation and read methods at three sites; 543 of the isolates were from indicated species which included the following: *C. freundii* (12 isolates), *C. koseri* (49 isolates), *K. aerogenes* (32 isolates), *E. cloacae* (48 isolates), *E. coli* (77 isolates), *K. oxytoca* (47 isolates), *K. pneumoniae* (89 isolates), *M. morganii* (41 isolates), *P. mirabilis* (56 isolates), *P. vulgaris* (17 isolates), *P. rettgeri* (19 isolates), *P. stuartii* (21 isolates), *S. marcescens* (32 isolates), *S. flexneri* (1 isolate), and *S. sonnei* (2 isolates). An additional 61 isolates of non-indicated *Enterobacteriaceae* isolates (approximately 10% of the total number of isolates tested) were also evaluated. The addition of the non-indicated species impacted but did not improve the performance calculated using indicated species alone.

A total of 19 clinical isolates of *Salmonella* spp. were evaluated including *S. enteritidis* (6 isolates), and *Salmonella* spp. (13 isolates).

A total of 79 clinical isolates of *P. aeruginosa* were evaluated with an appropriate mix of fresh isolates and recent isolates.

The clinical isolates evaluated represented an appropriate mix of fresh isolates (tested within one week of isolation), recent isolates (tested within six months of isolation with minimal subculturing and stock isolates (tested at any time after isolation).

Challenge isolates

A total of 85 *Enterobacteriaceae* challenge isolates were evaluated at one site. These included: *C. koseri, K. aerogenes, E. cloacae, E. coli, K. oxytoca, K. pneumoniae, M. morganii, P. mirabilis, P. rettgeri, S. marcescens, S. flexneri, S. sonnei* and 5 isolates of non-indicated species. In addition, two *Salmonella* ser. Typhi and 14 *P. aeruginosa* challenge isolates were evaluated. A single isolate of *S. flexneri* was excluded from the analysis of performance of the WalkAway read method due to the lack of results for this method.

Results for EA, CA and categorical errors for *Enterobacteriaceae, Salmonella* spp. and *P. aeruginosa* for all inoculation and read methods are shown in Tables 4 and 5 below. Overall

results for *Enterobacteriaceae*, *Salmonella* spp. and *P. aeruginosa* with all inoculation and read methods were acceptable.

Salmonella spp. results were evaluated separately from *Enterobacteriaceae* due to differences in susceptibility test interpretive criteria. In addition to the 21 clinical and challenge isolates of *Salmonella* spp. that were tested in this study, the previously cleared submission, K172912 was referenced to expand the evaluation of the performance of ciprofloxacin with *Salmonella* spp. Performance obtained with 74 isolates of *Salmonella* ser. Typhi evaluated with ciprofloxacin in K172912 (100% EA and CA for all inoculation and read methods) were considered in the evaluation of ciprofloxacin performance with members of this genus. The overall EA and CA performance for *Salmonella* spp. tested in the current study was acceptable for each inoculation and read method (Tables 4 and 5) and there were no major or very major errors. Based on the acceptable performance of ciprofloxacin for *Salmonella* species in these two submissions, the following previously imposed limitation (in K172912) was removed from the labeling associated with the current submission: *Ciprofloxacin labeled as Cp-S is not indicated for use for any species other than Salmonella Typhi.*

Table 4. Performance of MicroScan Dried Gram-Negative Panels with Ciprofloxacin, 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* – Breakpoints ≤0.25, 0.5, ≥1 µg/mL**													
Clinical	604	565	93.5	515	480	93.2	592	98.0	116	483	12	0	0
Challenge	84 [a]	81	96.4	60	57	95.0	82	97.6	30	51	2	0	0
Combined	688	646	93.9	575	537	93.4	674	98.0	146	534	14	0	0
***Salmonella* spp. – Breakpoints ≤0.06, 0.12 – 0.5, ≥1 µg/mL**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	2	2	100	1	1	100	1	50.0	1	1	1	0	0
Combined	21	21	100	20	20	100	20	95.2	1	18	0	0	0
***P. aeruginosa* – Breakpoints ≤0.5, 1, ≥2 µg/mL**													
Clinical	79	77	97.5	70	68	97.1	74	93.7	23	54	4	1	0
Challenge	14	13	92.9	13	12	92.3	11	78.6	6	4	3	0	0
Combined	93	90	96.8	83	80	96.4	85	91.4	29	58	7	1	0
autoSCAN-4 Read													
***Enterobacteriaceae* – Breakpoints ≤0.25, 0.5, ≥1 µg/mL**													
Clinical	604	568	94.0	515	482	93.6	593	98.2	116	483	11	0	0
Challenge	85	81	95.3	63	59	93.6	81	95.3	30	52	4	0	0
Combined	689	649	94.2	578	541	93.6	674	97.8	146	535	15	0	0
***Salmonella* spp. – Breakpoints ≤0.06, 0.12 – 0.5, ≥1 µg/mL**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	2	2	100	1	1	100	2	100	1	1	0	0	0
Combined	21	21	100	20	20	100	21	100	1	18	0	0	0
***P. aeruginosa* – Breakpoints ≤0.5, 1, ≥2 µg/mL**													
Clinical	79	74	93.7	70	65	92.9	68	86.1	23	54	9	1	1
Challenge	14	13	92.9	14	13	92.9	10	71.4	6	4	3	0	1
Combined	93	87	93.5	84	78	92.9	78	83.9	29	58	12	1	2

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	Vmj
Manual Read													
***Enterobacteriaceae* – Breakpoints ≤0.25, 0.5, ≥1 µg/mL**													
Clinical	604	565	93.5	516	483	93.6	592	98.0	116	483	12	0	0
Challenge	85	81	95.3	62	58	93.5	81	95.3	30	52	4	0	0
Combined	689	646	93.8	578	541	93.6	673	97.7	146	535	16	0	0
***Salmonella* spp. – Breakpoints ≤0.06, 0.12 – 0.5, ≥1 µg/mL**													
Clinical	19	19	100.0	19	19	100	19	100.	0	17	0	0	0
Challenge	2	2	100.0	1	1	100	1	50.0	1	1	1	0	0
Combined	21	21	100.0	20	20	100	20	95.2	1	18	0	0	0
***P. aeruginosa* – Breakpoints ≤0.5, 1, ≥2 µg/mL**													
Clinical	79	74	93.7	70	65	92.9	74	93.7	23	54	4	1	0
Challenge	14	14	100.0	14	14	100.	11	78.6	6	4	3	0	0
Combined	93	88	94.6	84	79	94.0	85	91.4	29	58	7	1	0

[a] No results recorded for one challenge isolate of *Shigella flexneri* with WalkAway

EA – Essential agreement
EVAL – Evaluable isolates
CA – Category agreement
R – Resistant
S – 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 Ciprofloxacin, 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* – Breakpoints ≤0.25, 0.5, ≥1 µg/mL**													
Clinical	604	580	96.0	514	493	95.9	595	98.5	116	483	9	0	0
Challenge	84[a]	83	98.8	62	61	98.4	80	95.2	30	51	4	0	0
Combined	688	663	96.4	576	554	96.2	675	98.1	146	534	13	0	0
***Salmonella spp.* – Breakpoints ≤0.06, 0.12 – 0.5, ≥1 µg/mL**													
Clinical	19	19	100	19	19	100	19	100	0	17	0	0	0
Challenge	2	2	100	1	1	100	1	50.0	1	1	1	0	0
Combined	21	21	100	20	20	100	20	95.2	1	18	0	0	0
***P. aeruginosa* – Breakpoints ≤0.5, 1, ≥2 µg/mL**													
Clinical	79	78	98.7	70	69	98.6	74	93.7	23	54	5	0	0
Challenge	14	13	92.9	14	13	92.9	11	78.6	6	4	3	0	0
Combined	93	91	97.8	84	82	97.6	85	91.4	29	58	8	0	0

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	mi n	maj	vmj
autoSCAN-4 Read													
***Enterobacteriaceae* – Breakpoints ≤0.25, 0.5, ≥1 µg/mL**													
Clinical	604	584	96.7	514	496	96.5	595	98.5	116	483	9	0	0
Challenge	85	82	96.5	63	60	95.3	80	94.1	30	52	5	0	0
Combined	689	666	96.7	577	556	96.4	675	98.0	146	535	14	0	0
***Salmonella spp.* – Breakpoints ≤0.06, 0.12 – 0.5, ≥1 µg/mL**													
Clinical	19	19	100.0	19	19	100.	19	100.0	0	17	0	0	0
Challenge	2	2	100.0	1	1	100.	1	50.0	1	1	1	0	0
Combined	21	21	100.0	20	20	100.	20	95.2	1	18	0	0	0
***P. aeruginosa* – Breakpoints ≤0.5, 1, ≥2 µg/mL**													
Clinical	79	74	93.7	70	65	92.9	71	89.9	23	54	7	0	1
Challenge	14	14	100.0	14	14	100.	11	78.6	6	4	3	0	0
Combined	93	88	94.6	84	79	94.0	82	88.2	29	58	10	0	1
Manual Read													
***Enterobacteriaceae* – Breakpoints ≤0.25, 0.5, ≥1 µg/mL**													
Clinical	604	578	95.7	515	493	95.7	596	98.7	116	483	8	0	0
Challenge	85	84	98.8	63	62	98.4	80	94.1	30	52	5	0	0
Combined	689	662	96.1	578	555	96.0	676	98.1	146	535	13	0	0
***Salmonella spp.* – Breakpoints ≤0.06, 0.12 – 0.5, ≥1 µg/mL**													
Clinical	19	19	100.0	19	19	100	19	100.0	0	17	0	0	0
Challenge	2	2	100.0	1	1	100	1	50.0	1	1	1	0	0
Combined	21	21	100.0	20	20	100	20	95.2	1	18	0	0	0
***P. aeruginosa* – Breakpoints ≤0.5, 1, ≥2 µg/mL**													
Clinical	79	78	98.7	70	69	98.6	75	94.9	23	54	4	0	0
Challenge	14	14	100.0	14	14	100	11	78.6	6	4	3	0	0
Combined	93	92	98.9	84	83	98.8	86	92.5	29	58	7	0	0

[a] No results recorded for one challenge isolate of *Shigella flexneri* with WalkAway see above

For *C. koseri, P. vulgaris, S. sonnei* and *Salmonella enteritidis,* 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 ciprofloxacin 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, Shigella sonnei and Salmonella enteritidis. Isolates yielding MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory.*

For tests inoculated using the Prompt Inoculation System, *E. cloacae* showed low essential agreement with all read methods, *K.* (*Enterobacter*) *aerogenes* showed low essential agreement with the WalkAway and Manual read method, *S. sonnei* showed low EA and CA (due to minor errors) and *S. marcescens* showed low essential agreement with the autoSCAN-4 and manual read methods. In addition, isolates of *C. koseri* inoculated with the turbidity inoculation method and read manually showed low essential agreement as compared to the reference method. The sponsor included the following limitation in the device labeling:

Results obtained with ciprofloxacin and E. cloacae with all read methods/Prompt, E. aerogenes with WalkAway/Prompt and manual/Prompt, S. sonnei with manual/Prompt and S. marcescens with the autoSCAN-4/Prompt and manual/Prompt have shown discrepant MICs when compared with the reference method. If critical to patient care, isolates of those species should be retested using the turbidity inoculation method. In addition, discrepant MICs were observed with ciprofloxacin and C. koseri with turbidity/manual read; if critical to patient care, isolates of C. koseri should be tested with an alternate inoculation/read method.

P. aeruginosa was observed to have lowered categorical agreement and an elevated very major error rate with the autoSCAN-4 read method and both turbidity and Prompt inoculation method during the initial clinical and challenge testing. Additional testing with *P. aeruginosa* challenge isolates was reviewed (29 isolates tested with Prompt and turbidity/auto-SCAN-4 and manual read methods, 23 isolates tested with Prompt and turbidity/WalkAway). Results of the original clinical and challenge testing combined with the additional challenge testing showed improved categorical agreement and very major error rate with turbidity inoculation and autoSCAN-4; an elevated very major error rate remained with Prompt/autoSCAN-4 (Table 6 below). The sponsor included the following limitation in the device labeling:

Due to low categorical agreement and increased occurrence of very major errors for P. aeruginosa and ciprofloxacin with the autoSCAN-4 and Prompt inoculation, results should be confirmed by manual read prior to reporting.

Table 6. Results of testing *P. aeruginosa* with all inoculation and read methods including additional challenge isolates.

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Prompt Inoculation													
WalkAway	116	113	97.4	91	88	96.7	113	97.4	46	64	8	1	0
autoSCAN-4	122	116	95.1	94	90	95.7	107	87.7	48	68	12	1	2
Manual	122	117	95.9	95	91	95.8	114	93.4	48	68	7	1	0
Turbidity Inoculation													
WalkAway	116	114	98.3	92	90	97.8	113	97.4	46	64	9	0	0
autoSCAN-4	122	117	95.9	95	91	95.8	111	91.0	48	68	10	0	1
Manual	122	121	99.2	96	95	99.0	115	94.3	48	68	7	0	0

Testing/Reporting MIC for Non-indicated Species:
For this review, the interpretative criteria are applied to the organisms/organism groups according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and Cosmetic Act, the following statement is added to the Warnings and Precautions section of the device labeling:

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.

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. Trending calculations for ciprofloxacin with *Enterobacteriaceae*, *Salmonella* spp., *P. aeruginosa* and species for which trending was observed are shown in Table 7 below.

To address the observed trending the sponsor included the following footnote to the performance table in the device labeling:

Ciprofloxacin MIC values for Enterobacteriaceae were most frequently in exact agreement with the reference method. When not in agreement results tended to be one doubling dilution higher for: C. freundii (Turbidity/WalkAway and manual read), C. koseri and Shigella sonnei (Prompt and Turbidity/all read methods), M. morganii (Prompt/WalkAway and manual read, Turbidity/manual read), Salmonella ser. Typhi (Prompt/WalkAway and manual read, Turbidity/WalkAway and manual read), and Salmonella spp. (Turbidity/WalkAway). MIC results for P. rettgeri tended to be one doubling dilution lower with Prompt and Turbidity inoculation with auto-SCAN-4.

Table 7. Trending Observed for Ciprofloxacin[a]

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***	**513**	**79 (15.4)**	**261 (50.9)**	**173 (33.7)**	**18.3 (13.1 to 23.4)**	**No**
	***Salmonella* spp.**	**20**	**0**	**16 (80.0)**	**4 (20.0)**	**20.0 (-0.1 to 41.6)**	**No**
	P. aeruginosa	**83**	**10 (12.1)**	**59 (71.1)**	**14 (16.9)**	**4.8 (-6.1 to 15.7)**	**No**
	C. koseri	51	1 (2.0)	15 (29.4)	35 (68.6)	66.7 (50.7 to 77.8)	Yes
	M. morganii	27	2 (7.4)	14 (51.9)	11 (40.7)	33.3 (10.6 to 52.6)	Yes
	S. sonnei	15	0	4 (26.7)	11 (73.3)	73.3 (40.9 to 89.1)	Yes
Prompt/ autoSCAN-4	***Enterobacteriaceae***	**517**	**123 (23.8)**	**264 (51.1)**	**130 (25.1)**	**1.4 (-3.9 to 6.6)**	**No**

Inoculation/ Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
	***Salmonella* spp.**	**20**	**0**	**19 (95.0)**	**1 (5.0)**	**5.0 (-11.6 to 23.6)**	**No**
	P. aeruginosa	**84**	**25 (29.8)**	**52 (61.9)**	**7 (8.3)**	**-21.4 (-32.7 to -9.7)**	**No**
	C. koseri	51	3 (5.9)	18 (35.3)	30 (58.8)	52.9 (36.0 to 66.0)	Yes
	P. rettgeri	19	9 (47.4)	9 (47.4)	1 (5.3)	-42.1 (-63.5 to -14.2)	Yes
	S. sonnei	15	1 (6.7)	4 (26.7)	10 (66.7)	60.0 (26.0 to 79.0)	Yes
Prompt/ Manual	***Enterobacteriaceae***	**517**	**82 (15.9)**	**255 (49.3)**	**180 (34.8)**	**19.0 (13.7 to 24.1)**	**No**
	***Salmonella* spp.**	**20**	**0**	**16 (80.0)**	**4 (20.0)**	**20.0 (-0.1 to 41.6)**	**No**
	P. aeruginosa	**83**	**11 (13.3)**	**50 (60.2)**	**22 (26.5)**	**13.3 (1.1 to 25.1)**	**No**
	C. koseri	51	2 (3.9)	10 (19.6)	39 (76.5	72.6 (56.4 to 82.5)	Yes
	M. morganii	28	2 (7.1)	15 (53.6)	11 (39.3)	32.1 (10.1 to 51.2)	Yes
	S. flexneri	8	0	5 (62.5)	3 (37.5)	37.5 (-2.7 to 69.4)	Yes[b]
	S. sonnei	15	0	5 (33.3)	10 (66.7)	66.7 (34.4 to 84.8)	Yes
Turbidity/ WalkAway	***Enterobacteriaceae***	**510**	**65 (12.8)**	**284 (55.7)**	**161 (31.6)**	**18.8 (13.8 to 23.7)**	**No**
	***Salmonella* spp.**	**20**	**0**	**14 (70.0)**	**6 (30.0)**	**30.0 (7.7 to 51.9)**	**Yes**
	P. aeruginosa	**84**	**16 (19.1)**	**58 (69.1)**	**10 (11.9)**	**-7.1**	**No**
	C. freundii	12	0	7 (58.3)	5 (41.7)	41.7 (8.7 to 68.1)	Yes
	C. koseri	51	1 (2.0)	13 (25.5)	37 (72.6)	70.6 (54.7 to 81.1)	Yes
	S. sonnei	15	0	5 (33.3)	10 (66.7)	66.7 (34.4 to 84.8)	Yes
Turbidity/ autoSCAN-4	***Enterobacteriaceae***	**509**	**117 (23.0)**	**284 (55.8)**	**108 (21.2)**	**-1.8 (-6.9 to 3.3)**	**No**
	***Salmonella* spp.**	**20**	**0**	**16 (80.0)**	**4 (20.0)**	**20.0 (-0.1 to 41.6)**	**No**
	P. aeruginosa	**84**	**31 (36.9)**	**47 (56.0)**	**6 (7.1)**	**-29.8 (-41.1 to -17.6)**	**No**
	C. koseri	51	4 (7.8)	21 (41.2)	26 (51.0)	43.1 (26.1 to 57.1)	Yes
	P. rettgeri	19	7 (36.8)	12 (63.2)	0	-36.8 (-59.0 to -12.4)	Yes
	S. sonnei	15	0	5 (33.3)	10 (66.7)	66.7 (34.4 to 84.8)	Yes
Turbidity/ Manual	***Enterobacteriaceae***	**517**	**74 (14.3)**	**274 (53.0**	**169 (32.7)**	**18.4 (13.3 to 23.4)**	**No**
	***Salmonella* spp.**	**20**	**0**	**16 (80.0)**	**4 (20.0)**	**20.0 (-0.1 to 41.6)**	**No**
	P. aeruginosa	**84**	**17 (20.2)**	**58 (69.1)**	**9 (10.7)**	**-9.5 (-20.5 to 1.6)**	**No**
	C. freundii	12	0	6 (50.0)	6 (50.0)	50.0 (15.4 to 74.6)	Yes
	C. koseri	51	1 (2.0)	13 (25.5)	37 (72.6)	70.6 (54.7 to 81.1)	Yes
	M. morganii	26	1 (3.9)	14	11	38.5 (15.9	Yes

Inoculation/ Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
				(53.9)	(42.3)	to 57.5)	
	S. flexneri	8	0	5 (62.5)	3 (37.5)	37.5 (-2.7 to 69.4)	Yes[b]
	S. sonnei	15	0	5 (33.3)	10 (66.7)	66.7 (34.4 to 84.8)	Yes

[a] See K172912 for trending results for *Salmonella* ser.Typhi
[b] Not statistically significant

Resistance Mechanism Characterization
Challenge isolates of *Enterobacteriaceae* and *P. aeruginosa* harboring various molecular mechanisms of resistance were tested with ciprofloxacin. Isolates from the CDC and FDA Antibiotic Resistance Isolate Bank were evaluated. No isolates harboring *gyr*A, *gyr*B, *par*C or *par*E were tested.

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-recognized breakpoints for ciprofloxacin are shown in Table 8 below.

Table 8. FDA-Recognized Interpretive Criteria for Ciprofloxacin

Organism	Interpretive Criteria for Ciprofloxacin MIC (µg/mL)[a]		
	Susceptible	Intermediate	Resistant
Enterobacteriaceae	**≤0.25**	**0.5**	**≥1**
***Salmonella* spp.**	**≤0.06**	**0.12 -0.5**	**≥1**
P. aeruginosa	**≤0.5**	**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 Ciprofloxacin (Cp) (0.004 – 8 µg/mL) when revised breakpoints for ciprofloxacin 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 ciprofloxacin 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.