510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K172912

B. Purpose for Submission:

To obtain a substantial equivalence determination for Ciprofloxacin at concentrations of 0.004-8µg/mL on the MicroScan Dried Gram-Negative MIC/Combo Panels for susceptibility testing of *Salmonella* Typhi based on the new FDA breakpoint change.

C. Measurand:

Ciprofloxacin in the dilution range of 0.004-8 µg/mL

D. Type of Test:

Quantitative and/or qualitative Antimicrobial Susceptibility Test (AST).

E. Applicant:

Beckman Coulter

F. Proprietary and Established Names:

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

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product codes:

   LTT – Panels, Test, Susceptibility, Antimicrobial

   JWY – Manual Antimicrobial Susceptibility Test Systems

LRG – Instrument for Auto Reader and Interpretation of Overnight Susceptibility Systems

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended use(s):

   For use with MicroScan Dried Gram Negative MIC/Combo Panels and Dried Gram Negative Breakpoint Combo panels. MicroScan panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of aerobic and facultatively anaerobic gram-negative bacilli.

2. 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 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 the addition of the antimicrobial ciprofloxacin at concentrations of 0.004 to 8 µg/mL to the test panel.

   The gram-negative organism which may be used for ciprofloxacin susceptibility testing on this panel is:

   Salmonella Typhi

3. Special conditions for use statement(s):

   For prescription use only.

   Limitation:

   "Ciprofloxacin labeled as Cp-S is not indicated for use for any species other than Salmonella Typhi"

4. Special instrument requirements:

   MicroScan panels can be read either manually or automatically on the WalkAway or

autoScan-4 instrument systems.

I. 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 colonies grown on solid media. The panel is used for testing rapidly growing aerobic and facultative gram-negative bacilli. After inoculation, panels are incubated for 16-20 hours at 35°C ± 1°C in a non-CO2 incubator and read either visually or with MicroScan instrumentation according to the package insert.

Inoculation methods: Turbidity, Prompt Inoculation System

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

J. Substantial Equivalence Information:

1. Predicate device name(s):

   MicroScan Dried Gram-Negative MIC/Combo Panels – Imipenem

2. Predicate 510(k) number(s):

   K162740

3. Comparison with predicate:

Table 1. Comparison with the Predicate

Similarities		
Item	Device, Ciprofloxacin (K172912)	Predicate, Imipenem (K162740)
Intended Use	Determination of susceptibility to ciprofloxacin with gram-negative bacteria (*Salmonella* Typhi only)	Determination of susceptibility to imipenem with gram-negative bacteria
Technology	Overnight microdilution MIC susceptibility Test	Same
Specimen	Isolated colonies from cultures	Same
Incubation Temperature	35°C±1°C	Same
Incubation Atmosphere	Aerobic	Same
Incubation Time	16-20 hours	Same

Similarities		
Item	Device, Ciprofloxacin (K172912)	Predicate, Imipenem (K162740)
Result Reported	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (S I R)	Same
Read Methods	Manual and automated	Same
Inoculation Methods	Turbidity and Prompt	Same
Instrumentation	WalkAway or autoSCAN-4 Instrument systems	Same

Differences		
Item	Device	Predicate
Antimicrobial agent	Dried Ciprofloxacin 0.004 – 8 µg/mL	Dried Imipenem 0.25 – 8 µg/mL

K. Standard/Guidance Document Referenced (if applicable):

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA
2. CLSI M7-A10. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, January, 2015.
3. CLSI M100-S27. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement.

L. Test Principle:

The antimicrobial susceptibility tests are miniaturizations of the broth dilution susceptibility test which have been dehydrated. Various antimicrobial agents are diluted in Mueller Hinton broth supplemented with calcium and magnesium to concentrations bridging the range of clinical interest. Breakpoint Combo panels use concentrations equivalent to the categorical breakpoints of FDA and/or CLSI. After inoculation and rehydration with a standardized suspension of organism and incubation of 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was conducted at three sites using 11 different strains of *Salmonella* Typhi. Isolates were tested in triplicate over three days for a total of 297 data points. Inocula were prepared using both the turbidity and Prompt method and

results were read manually and automatically with the WalkAway and autoSCAN-4 instrument systems. The mode of MIC value was pre-determined and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode. The testing resulted in overall reproducibility of greater than 95% for all inoculum preparation and reading methods.

The reproducibility results were acceptable.

b. *Linearity/assay reportable range:*

Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Inoculum Density Check. A spectrophotometric device, the MicroScan Turbidity Meter) was used to ensure quality control of the turbidity inoculum method. The turbidity inocula were prepared using the MicroScan Turbidity Meter with a reading of 0.08 ± 0.02 (equivalent to a 0.5 McFarland barium sulfate turbidity standard). The digital reading was recorded each day of use.

Data was also collected during the Reproducibility phase using the Prompt inoculum preparation method.

Colony counts were performed weekly on the quality control strain *E. coli* ATCC 25922. Colony counts were also done once at each site for each reproducibility isolate.

Purity Check. Purity check plates were performed on all isolates from each inoculum preparation.

Growth Failure Rate. During the course of the study there were no growth failures with the MicroScan or the frozen reference panel with Ciprofloxacin.

Quality Control Testing. The CLSI and FDA recommended QC organisms (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) were tested using all inoculation and read methods against Ciprofloxacin at four sites (three external and one internal site). Results obtained with the frozen reference panel and Test panel were compared to the expected range of each strain. The results are summarized in Tables 2 and 3.

Table 2. Quality Control Results with *E. coli*, ATCC 25922

Organism	Conc (µg/mL)	Ref	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
E. coli ATCC 25922 Expected Range 0.004-0.015 µg/mL	**≤0.004**	2	66	40	149			
	0.008	175	122	144	38	40	13	131
	0.015	12				148	175	57
	0.03							
	0.06					1	1	
	0.12							
	0.25		1	1	1			
	0.5							
	1							
	2							
	4							
	8							

Table 3. Quality Control Results with *P. aeruginosa*, ATCC 27853

Organism	Conc (µg/mL)	Ref	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
P. aeruginosa ATCC 27853 Expected Range 0.25-1µg/mL	**0.004**							
	0.008							
	0.015							
	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							

Quality control results with *E. coli* ATCC 25922 and *P. aeruginosa*, ATCC 27853 met the acceptance criteria of > 95% agreement with the expected value for all inoculation and read methods and demonstrated that the system could produce the expected quality control results.

The quality control results are acceptable.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Results obtained with the MicroScan Dried Gram-Negative MIC/Combo Panel with Ciprofloxacin were compared to results obtained with the CLSI frozen broth microdilution reference panel. Reference panels were prepared according to the CLSI Document M7-A10 (Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Tenth Edition. Pennsylvania, CLSI, 2015), using cation adjusted Mueller-Hinton broth. The reference panels were read visually after 16-20 hours of incubation at 35 ± 1° C in a non-CO_2 incubator.

The range of dilutions evaluated with the MicroScan panels was 0.004 – 8 µg/mL. The frozen reference panel also contained those 12 dilutions of Ciprofloxacin.

Two inoculation methods were used: the Prompt Inoculation System and the turbidity method. For the Prompt Inoculation System (the primary method), inocula were prepared using the instructions of the manufacturer. For the turbidity method, inocula were standardized using the MicroScan Turbidity Meter to approximate a 0.5 McFarland turbidity standard. Reference panels were inoculated using the turbidity method.

Three read methods were evaluated: manual read, automated read using the WalkAway and automated read using the autoScan-4. Reference panels were manually read.

As agreed upon in pre-submission Q160981, an attempt was made to collect freshly recovered clinical isolates but there were no incidences of fresh *Salmonella* Typhi isolates due to rare occurrence of these infections in the US. Theredore, a total of 74 gram-negative challenge isolates were tested at three external study sites. Of the 74 *Salmonella* Typh*i* strains tested, 18 isolates were susceptible and 26 were resistant to Ciprofloxacin by the reference method.

For the primary method, WalkAway instrument read and Prompt inoculation, the *Salmonella* Typhi results from the Challenge study demonstrated an overall EA of 100% (74/74) and a CA of 94.6% (70/74). There were 4 minor discrepencies (5.4%) and no major or very major discrenpencies. The overall performance is acceptable.

Table 4 below summarize the performance with Ciprofloxacin for *Salmonella* Typhi. Data is shown for each inoculum preparation method (Prompt and turbidity) and for each read method (WalkAway, autoSCAN-4 and manual read).

Table 4. Performance of MicroScan Dried Gram-Negative Panels with Ciprofloxacin with *Salmonella* Typhi, Prompt and Turbidity Inoculation Method, 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													
Prompt	74	74	100	55	55	100	70	94.6	26	18	4	0	0
Turbidity	74	74	100	55	55	100	71	95.9	26	18	3	0	0
autoSCAN-4													
Prompt	74	74	100	56	56	100	72	97.3	26	18	2	0	0
Turbidity	74	74	100	56	56	100	71	95.9	26	18	3	0	0
Manual													
Prompt	74	74	100	55	55	100	70	94.6	26	18	4	0	0
Turbidity	74	74	100	55	55	100	71	95.9	26	18	3	0	0

EA – Essential Agreement (+/- 2 dilutions)
CA – Category Agreement
EVAL – Evaluable isolates
R or NS – Resistant or non-susceptible isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of the MicroScan panel within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the MicroScan panel and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the MicroScan panel.

MIC Trend Analysis

Using the data provided by the sponsor in the diagonal table format recommended in the AST Special Controls guidance document, an analysis was conducted for trending in MIC values for each inoculation and reading 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 whether the device MIC values are on-scale or not. As summarized in Tables 5-6 below, a higher trending was observed with *Salmonella* Typhi with both inoculation methods and all reading methods

Table 5. Trending of Results by Prompt Inoculation Method

Reading Methods	Difference in MIC as Compared to the CLSI Reference Method						Percent Difference in Trending between the higher and lower dilutions*
	# Eval Isolates for Trending	≤2 dil. Lower	1 dil. Lower	Exact	1 dil. Higher	≥2 dil. Higher	
WalkAway	57	0	1	36 (63.16%)	20	0	33.33% 95% CI: 19.93% 46.38%
		1 (1.75%)			20 (35.09%)		
AutoScan	57	0	2	39 (68.42%)	16	0	24.56% 95% CI: 11.50% 37.57%
		2 (3.51%)			16 (28.07%)		
Manual	57	0	1	34 (59.65%)	22	0	36.84% 95% CI: 23.06% 49.90%
		1 (1.75%)			22 (38.60%)		

***Note:** A positive percent difference value indicates higher MIC when compared to the reference method.

Table 6. Trending of Results by Turbidity Inoculation Method

Reading Methods	Difference in MIC as Compared to the CLSI Reference Method						Percent Difference in Trending*
	# Eval Isolates for Trending	≤2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher	
WalkAway	57	0	0	35 (61.40%)	22	0	38.60% 95% CI: 25.45% 51.57%
		0 (0%)			22 (38.60%)		
AutoScan	57	0	1	38 (66.67%)	18	0	29.82% 95% CI: 16.84% 42.81%
		1 (1.75%)			18 (31.58%)		
Manual	57	0	0	34 (59.65%)	23	0	40.35% 95% CI: 27.03% 53.30%
		0 (0%)			23 (40.35%)		

***Note:** A positive percent difference value indicates higher MIC when compared to the reference method.

A higher MIC reading trend was observed in the overall performance of *S.* Typhi with both inoculation methods (Prompt and Turbidity) and with all reading methods (WalkAway, AutoScan and Manual) when compared to the CLSI broth microdilution reference method, which raises concerns for potential major discrepancies. This trending and the potential for occurrence of major discrepancies were addressed by adding the following footnote to the labeling:

"Ciprofloxacin-S MIC values tended to be one dilution higher when compared to the reference broth microdilution method for S. Typhi".

Prompt Hold Study
An additional study was performed using 20 *Salmonella* Typhi at one site to determine the agreement of results obtained with the Prompt inoculation method using hold times of 0 hours and 4 hours prior to inoculation of the panels. The following times and comparisons were made with each of the read methods (WalkAway, autoSCAN-4 and manual).

Results of 4-hour hold vs. results of 0-hour hold

Results of 4-hour hold vs. results obtained with the frozen reference method

Results of 0-hour hold vs. results obtained with the frozen reference method

All tests showed overall acceptable essential agreement; category agreement was >95.0% with all read methods. There were no major or very major errors. There was only 1 minor error out of 20 (5% minor error rate)with the WalkAway and the manual reading reading methods when compared to the frozen reference method.

Results were determined to be acceptable.

b. Matrix comparison:

Not Applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not Applicable

b. Clinical specificity:

Not Applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Ciprofloxacin are as listed in Table 7.

Table 7. FDA Interpretive Criteria for Ciprofloxacin (µg/mL)

Organism	FDA Interpretive Criteria for Ertapenem MIC (µg/mL)		
	S	I	R
Salmonella Typhi	≤0.06	0.12-0.5	≥1

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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