510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K243804

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64 µg/mL) (MicroScan)

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 the MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64 µg/mL) with a revised formulation of cefepime and updated FDA-recognized breakpoints.

B Measurand:

Cefepime in the dilution range of 0.12-64 µg/mL

C Type of Test:

Quantitative antimicrobial susceptibility test (AST)

III Intended Use/Indications for Use:

A 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.

B Indication(s) for Use:
The MicroScan Dried Gram-Negative MIC/Combo Panel is used to determine quantitative and 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-CO2 incubator, and read either visually or with MicroScan instrumentation, according to the Package Insert.

This particular submission is for the addition of the antimicrobial cefepime at concentrations of 0.12-64 µg/mL to the test panel. Testing is indicated for Enterobacterales, *Pseudomonas aeruginosa* and *Aeromonas* spp., as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC) webpage.

The MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64µg/mL) has demonstrated acceptable performance with the following organisms:

Enterobacterales (*Enterobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter koseri*, (formerly *Citrobacter diversus*), *Citrobacter freundii* complex (*Citrobacter freudnii*, *Citrobacter werkmanii* and *Citrobacter youngae*), *Klebsiella oxytoca*, *Morganella morganii*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia rettgeri*, *Serratia marcescens*)

Pseudomonas aeruginosa

Aeromonas spp.

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

Results obtained with Enterobacterales and cefepime for all read methods with the Prompt inoculation system were outside of essential agreement when compared to the reference method. If critical to patient care, Enterobacterales should be retested using the Turbidity inoculation method.

Elevated MICs with cefepime may be observed if panels are over-inoculated with Enterobacterales microorganisms (e.g., M. morganii, Enterobacter spp., K. oxytoca, S. marcescens) across all read methods. Inoculum concentration is critical with cefepime, therefore, the user should pay careful attention to inoculum preparation, especially with manual methods that are technique dependent such as the Prompt system or inoculum prepared without the aid of a photometric device.

Results obtained with cefepime and H. alvei have shown discrepant MIC's when compared with an overnight reference method. Test results for these organisms will not be reported, and an alternate method for testing should be used.

Performance of cefepime when testing Aeromonas spp. using the Turbidity inoculation method with the WalkAway read method were within essential agreement, but outside of categorical agreement due to the elevated very major error rate and minor errors when compared to the reference method. Aeromonas spp. results with the Turbidity/WalkAway should be read manually prior to reporting.

Due to the occurrence of one major error with C. freundii complex and cefepime with Turbidity inoculation and all read methods, MIC results of 32 µg/mL should be confirmed by an alternate method prior to reporting.

The ability of the MicroScan Dried Gram Negative Panels to detect resistance to cefepime is unknown with C. koseri because an insufficient number of resistant strains were available at the time of comparative testing. Isolates yielding MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory.

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 cefepime 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 Ceftazidime (Caz) (0.5-64 µg/mL)

B Predicate 510(k) Number(s):
K202343

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K243804	Predicate: K202343
Device Trade Name	MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64 µg/mL)	MicroScan Dried Gram-Negative MIC/Combo Panels with Ceftazidime (Caz) (0.5-64 µg/mL)
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 Cefepime 0.12-64 µg/mL	Dried Ceftazidime 0.5-64 µg/mL
Tested species	Enterobacterales (*Enterobacter* spp., *Escherichia coli,*	*Citrobacter* species, *Enterobacter* species,

	Klebsiella pneumoniae, Proteus mirabilis, Citrobacter koseri, Citrobacter freundii complex *(Citrobacter freudnii, Citrobacter werkmanii* and *Citrobacter youngae), Klebsiella oxytoca, Morganella morganii, Proteus vulgaris, Providencia stuartii, Providencia rettgeri, Serratia marcescens), Pseudomonas aeruginosa, Aeromonas* spp.	*Escherichia coli, Klebsiella* species*, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Serratia* species*, Acinetobacter* species*, Citrobacter koseri, Citrobacter freundii, Salmonella* species*, Shigella* species*, Yersinia enterocolitica*

VI Standards/Guidance Documents Referenced:

CLSI M07, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Eleventh Edition", (January 2018)

CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing; 35th Edition", (January 2025)

CLSI M45-3rd Edition, "Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria", (August 2016)

Guidance for Industry and FDA: Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems, August 28, 2009

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study was conducted at three clinical sites using 10 isolates of gram-negative isolates that were consistent with the device intended use. The range of cefepime dilutions tested was 0.12-64 µg/mL. Isolates were tested in triplicate over three days at three of the four clinical sites (27 data points per isolate) for a total of 270 data points. The isolates tested in the reproducibility study included: *E. coli* (1 isolate), *K. pneumoniae* (1 isolate), and *P. aeruginosa* (8 isolates).

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 mode (or median for results without a mode) of MIC values was determined for each isolate and the reproducibility was calculated based on the number of MIC values that fell within ± one doubling dilution of the mode/median MIC value. The majority of data points were within ± one doubling dilution of the mode/median MIC value. The data were analyzed as described in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST)*

Systems. For those read/inoculation combinations that included off-scale results, reproducibility was assessed as best-case and worst-case scenarios (**Table 1**).

Table 1. Reproducibility of Cefepime with all Inoculation and Read Methods

Read Method	Reproducibility No. within ± one dilution of the mode/median MIC value (%)			
	Prompt Inoculation		Turbidity Inoculation	
	Best	Worst	Best	Worst
WalkAway	265/270 (98.1)	265/270 (98.1)	264/270 (97.8)	264/270 (97.8)
autoSCAN-4	264/270 (97.8)	264/270 (97.8)	266/270 (98.5)	266/270 (98.5)
Manual	265/270 (98.1)	265/270 (98.1)	266/270 (98.5)	266/270 (98.5)

Reproducibility performance was considered acceptable for all inoculation and read 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):

   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 was collected for the Prompt inoculum preparation of all reproducibility isolates and weekly testing of QC strain *E. coli* ATCC 25922, as well as monthly QC testing with the Turbidity inoculation method. The overall average colony count was within the acceptable range for all isolates.

   Evaluation of the Prompt inoculum effect.
   In the clinical study, the unacceptable EA (<90%) with some Enterobacterales species was observed specifically with the Prompt inoculation method, while the same species performed acceptably with the Turbidity inoculation method. These findings suggested a Prompt-

specific inoculum effect based on performance differences between the two inoculation methods. To further evaluate a potential inoculum effect observed when testing cefepime/Enterobacterales using the Prompt inoculation system across all read methods (i.e., autoSCAN-4, Manual, and WalkAway read methods) in the clinical study, thirty (30) randomly selected fresh/contemporary Enterobacterales isolates from the clinical study were re-tested. Testing was conducted on MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64 µg/mL) using the Prompt inoculation system concurrently with a frozen broth microdilution reference panel (dilution range 0.12-64 µg/mL) prepared using the Turbidity inoculation method. Inoculum density data were collected for each selected clinical isolate using both methods.

Colony count analysis revealed statistically significant higher colony counts from the Prompt inoculation method (Average: 1.29E+06 CFU/mL) compared to the Turbidity inoculation method (Average: 2.94E+05 CFU/mL), with a paired Student's t-test p-value of <0.0001.

In addition, performance comparison was conducted to evaluate the MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime in comparison to the frozen broth microdilution reference panel. Performance data demonstrated that essential agreement for Enterobacterales MICs obtained with Prompt inoculation across all read methods was below 90% (ranging from 63.3% to 76.7% depending on read method). When stratified by individual species, EA performance was more variable, with EA rates potentially reaching 0% for certain species given the limited number of isolates tested per species (1-6 isolates each). These observations reinforce the concern regarding unacceptable performance of the Prompt inoculum method for Enterobacterales and indicated a possible Prompt inoculum effect adversely affecting performance of the MicroScan Dried Gram-Negative MIC/Combo Panels for Cefepime/Enterobacterales when using the Prompt inoculation system. This is addressed with the following specific limitation:

> *Results obtained with Enterobacterales and cefepime for all read methods with the Prompt inoculation system were outside of essential agreement when compared to the reference method. If critical to patient care, Enterobacterales should be retested using the Turbidity inoculation method.*

In addition, another limitation was included in device labeling which restricts reporting the results obtained with Enterobacterales and cefepime for all read methods with the Prompt inoculation method was also included:

> *Elevated MICs with cefepime may be observed if panels are over-inoculated with Enterobacterales microorganisms (e.g., M. morganii, Enterobacter spp., K. oxytoca, S. marcescens) across all read methods. Inoculum concentration is critical with cefepime, therefore, the user should pay careful attention to inoculum preparation, especially with manual methods that are technique dependent such as the Prompt system or inoculum prepared without the aid of a photometric device.*

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

Growth Failure Rate. During the clinical study, no isolates failed to grow on the dried test panels and frozen reference panel which is acceptable (<10% growth failure).

Quality Control Testing. The CLSI-recommended QC organism *P. aeruginosa* ATCC 27853 was tested with all inoculation and read methods using 10 dilutions of cefepime (0.12-64 µg/mL). The reference panel was inoculated using the turbidity method only. In this submission, the QC range for *P. aeruginosa* reflects the current MIC ranges recommended in the CLSI document M100, *Performance Standards for Antimicrobial Susceptibility Testing* 34th ed. The results of QC testing are shown in **Table 2**. Quality control results were within the acceptable range for all inoculation and read methods for ≥95% of tests which is acceptable.

Table 2. Quality Control Results for all Inoculation and Read Methods for Cefepime

Organism	Conc. (µg/mL)	Reference [1]	Prompt Inoculation Method			Turbidity Inoculation Method		
			autoSCAN-4	Manual	WalkAway	autoSCAN-4	Manual	WalkAway
P. aeruginosa ATCC 27853 Expected Range 0.5–4 µg/mL	≤ 0.12							
	0.25							
	0.5	1	1			1		1
	1	82	68	68	64	77	78	73
	2	9	21	22	23	14	14	17
	4	1	1	1	1	1	1	2
	8		1	1	2			
	16				1			
	32				1			
	64		1	1	1			
	> 64							

[1] Frozen reference panel inoculated using the turbidity method and interpreted manually.

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 Panels with Cefepime (0.12-64 µg/mL) were compared to results obtained using a frozen broth microdilution reference panel (dilution range 0.12-64 µg/mL). Clinical isolates were evaluated at three testing sites in the U.S. and challenge isolates were evaluated at one site.

   The reference panel was prepared as described in CLSI document M07-A11 except for the use of Pluronic-F (wetting agent) in the inoculum water for the reference panel. A summary of historical data from previously cleared antimicrobial tests was provided in the submission which demonstrated that inclusion of the wetting agent did not affect testing. In addition, QC testing 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 inoculum 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) after 16-20 hours. MicroScan panels inoculated with both inoculation methods were read using the WalkAway and autoSCAN-4 instruments and by manual read after 16-20 hours.

Clinical Study
To determine the performance of the MicroScan Dried Gram-Negative MIC/Combo Panel with Cefepime, a total of 515 gram-negative clinical isolates [Enterobacterales (439 isolates), *P. aeruginosa* (45 isolates) and *Aeromonas* spp. (31 isolates)] were evaluated with the Prompt inoculation method and the Turbidity inoculation method and all read methods at three sites. The Enterobacterales isolates tested include the following species: *C. freundii* complex (*C. freundii* 30 isolates; *C. werkmanii* 1 isolate and *C. youngae* 1 isolate), *C. koseri* (30 isolates), *Enterobacter* spp. (54 isolates), *E. coli* (30 isolates), *H. alvei* (4 isolates), *K. aerogenes* (30 isolates), *K. oxytoca* (30 isolates), *K. pneumoniae* (30 isolates), *L. adecarboxylata* (1 isolate), *M. morganii* (32 isolates), *P. mirabilis* (31 isolates), *P. vulgaris* (30 isolates), *P. alcalifaciens* (1 isolate), *P. rettgeri* (30 isolates), *P. stuartii* (30 isolates), *S. marcescens* (28 isolates) and *Y. enterocolitica* (16 isolates).

Performance when testing *H. alvei* was not acceptable, and only a low number of isolates (n=4) were available in the clinical study. These isolates were excluded from the Indications for Use for the MicroScan Dried Gram-Negative MIC/Combo Panel with Cefepime and excluded from the clinical study analysis. In addition, four isolates were excluded from the Prompt inoculation method due to colony morphology (e.g., small colony, mucoid isolate not adhering to the Prompt wand). As such, results of 507 clinical isolates [Enterobacterales (431 isolates), *P. aeruginosa* (45 isolates) and *Aeromonas* spp. (31 isolates)] and 511 clinical isolates [Enterobacterales (435 isolates), *P. aeruginosa* (45 isolates) and *Aeromonas* spp. (31 isolates)] were included in the performance evaluation for the Prompt and Turbidity inoculation methods, respectively. This is addressed with the following limitations in the device labeling:

> *Results obtained with the Hafnia alvei and cefepime have shown discrepant MIC's when compared with an overnight reference method. Test results for these organisms will not be reported, and an alternate method for testing should be used.*
>
> *Some mucoid strains of organisms such as Klebsiella spp. or Pseudomonas spp. may not adhere to the Prompt wand when attempting to pick the colony. This will be visually apparent. An alternate method of inoculum preparation should be used for such organisms.*

Challenge Study
A total of 80 gram-negative challenge isolates from species with STIC-recognized breakpoints were evaluated at two sites. Isolates included Enterobacterales [55 isolates; *C. freundii* complex (2 isolates), *E. coli* (23 isolates), *K. oxytoca* (2 isolates), *K. pneumoniae* (24

isolates), *M. morganii* (2 isolates), *P. mirabilis* (1 isolate), *S. marcescens* (1 isolate)] and *P. aeruginosa* (25 isolates)].

Results for essential agreement, categorical agreement, and categorical errors for Enterobacterales, *P. aeruginosa* and *Aeromonas* spp. for all inoculation and read methods are shown in **Table 3** and **Table 4** 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. Performance was evaluated separately for each organism group (i.e., Enterobacterales, *P. aeruginosa* and *Aeromonas* spp.) in accordance with the appropriate susceptibility test interpretive criteria for each group. Data for all species within a group were analyzed for performance separately and combined in accordance with the STIC-recognized breakpoints for the group then presented combined as shown in **Table 3** and **Table 4**. Footnotes and limitations were applied in labeling as appropriate.

Table 3. Performance of MicroScan Dried Gram-Negative Panels with Cefepime, Using *Prompt* Inoculation and all Read Methods

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
autoSCAN-4 Read													
Enterobacterales, ≤2 (S), 4-8 (SDD*), ≥16 (R)													
Clinical	431	385	89.3	85	39	45.9	409	94.9	30	390	15	7	0
Challenge	55	50	90.9	11	6	54.6	51	92.7	48	3	4	0	0
Combined	486	435	89.5	96	45	46.9	460	94.7	78	393	19	7	0
***Pseudomonas aeruginosa*, ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	45	44	97.8	45	44	97.8	40	88.9	1	37	5	0	0
Challenge	25	23	92.0	19	17	89.5	23	92.0	13	10	2	0	0
Combined	70	67	95.7	64	61	95.3	63	90.0	14	47	7	0	0
***Aeromonas* spp., ≤ 2 (S), 4-8 (I), ≥16 (R)**													
Clinical	31	29	93.6	9	7	77.8	28	90.3	6	23	2	0	1
Combined	31	29	93.6	9	7	77.8	28	90.3	6	23	2	0	1
Manual Read													
Enterobacterales, ≤2 (S), 4-8 (SDD), ≥16 (R)													
Clinical	431	383	88.9	86	38	44.2	409	94.9	30	390	17	5	0
Challenge	55	50	90.9	11	6	54.6	51	92.7	48	3	4	0	0
Combined	486	433	89.1	97	44	45.4	460	94.7	78	393	21	5	0
***Pseudomonas aeruginosa*, ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	45	44	97.8	45	44	97.8	41	91.1	1	37	4	0	0
Challenge	25	23	92.0	19	17	89.5	23	92.0	13	10	2	0	0
Combined	70	67	95.7	64	61	95.3	64	91.4	14	47	6	0	0
***Aeromonas* spp., ≤ 2 (S), 4-8 (I), ≥16 (R)**													
Clinical	31	29	93.6	9	7	77.8	28	90.3	6	23	2	0	1
Combined	31	29	93.6	9	7	77.8	28	90.3	6	23	2	0	1
WalkAway Read													
Enterobacterales, ≤2 (S), 4-8 (SDD), ≥16 (R)													
Clinical	431	360	83.5	106	35	33.0	407	94.4	30	390	16	8	0
Challenge	55	50	90.9	11	6	54.6	51	92.7	48	3	4	0	0
Combined	486	410	84.4	117	41	35.0	458	94.2	78	393	20	8	0
***Pseudomonas aeruginosa*, ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	45	44	97.8	45	44	97.8	41	91.1	1	37	4	0	0
Challenge	25	23	92.0	19	17	89.5	23	92.0	13	10	2	0	0
Combined	70	67	95.7	64	61	95.3	64	91.4	14	47	6	0	0

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
***Aeromonas* spp., ≤ 2 (S), 4-8 (I), ≥16 (R)**													
Clinical	31	29	93.5	9	7	77.8	28	90.3	6	23	2	0	1
Combined	31	29	93.5	9	7	77.8	28	90.3	6	23	2	0	1

*SDD- Susceptible-dose dependent.

EA – Essential agreement
CA – Category agreement
EVAL – Evaluable isolates
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. 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 4. Performance of MicroScan Dried Gram-Negative Panels with Cefepime, Using *Turbidity* Inoculation and all Read Methods

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
autoSCAN-4 Read													
Enterobacterales, ≤2 (S), 4-8 (SDD*), ≥16 (R)													
Clinical	435	411	94.5	67	43	64.2	417	95.9	30	393	16	2	0
Challenge	55	54	98.2	14	13	92.9	54	98.2	48	3	1	0	0
Combined	490	465	94.9	81	56	69.1	471	96.1	78	396	17	2	0
***Pseudomonas aeruginosa*, ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	45	44	97.8	45	44	97.8	42	93.3	1	37	3	0	0
Challenge	25	25	100.0	19	19	100.0	24	96.0	13	10	1	0	0
Combined	70	69	98.6	64	63	98.4	66	94.3	14	47	4	0	0
***Aeromonas* spp., ≤ 2 (S), 4-8 (I), ≥16 (R)**													
Clinical	31	31	100.0	8	8	100.0	27	87.1	6	23	4	0	0
Combined	31	31	100.0	8	8	100.0	27	87.1	6	23	4	0	0
Manual Read													
Enterobacterales, ≤2 (S), 4-8 (SDD), ≥16 (R)													
Clinical	435	413	94.9	68	46	64.8	417	95.9	30	393	16	2	0
Challenge	55	54	98.2	14	13	92.9	54	98.2	48	3	1	0	0
Combined	490	467	95.3	82	59	69.4	471	96.1	78	396	17	2	0
***Pseudomonas aeruginosa*, ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	45	44	97.8	45	44	97.8	43	95.6	1	37	2	0	0
Challenge	25	25	100.0	19	19	100.0	24	96.0	13	10	1	0	0
Combined	70	69	98.6	64	63	98.4	67	95.7	14	47	3	0	0
***Aeromonas* spp., ≤ 2 (S), 4-8 (I), ≥16 (R)**													
Clinical	31	31	100.0	8	8	100.0	27	87.1	6	23	4	0	0
Combined	31	31	100.0	8	8	100.0	27	87.1	6	23	4	0	0
WalkAway Read													
Enterobacterales, ≤2 (S), 4-8 (SDD), ≥16 (R)													
Clinical	435	410	94.3	71	46	64.8	417	95.9	30	393	14	3	1
Challenge	55	54	98.2	14	13	92.9	55	100.0	48	3	0	0	0
Combined	490	464	94.7	85	59	69.4	472	96.3	78	396	14	3	1
***Pseudomonas aeruginosa*, ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	45	44	97.8	45	44	97.8	44	97.8	1	37	1	0	0
Challenge	25	24	96.0	19	18	94.7	24	96.0	13	10	1	0	0
Combined	70	68	97.1	64	62	96.9	68	97.1	14	47	2	0	0
***Aeromonas* spp., ≤ 2 (S), 4-8 (I), ≥16 (R)**													

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Clinical	31	30	96.8	8	7	87.5	27	87.1	6	23	3	0	1
Combined	31	30	96.8	8	7	87.5	27	87.1	6	23	3	0	1

*SDD- Susceptible-dose dependent.

EA – Essential agreement
CA – Category agreement
EVAL – Evaluable isolates
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. 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.

Enterobacterales

The overall EA and CA performance for Enterobacterales for the Turbidity inoculation method and all read methods (i.e., autoSCAN-4, Manual, and WalkAway read methods) were acceptable. The overall Enterobacterales EA was < 90% for all three read methods when inoculated with the Prompt inoculation method, which is not acceptable. Additionally, when analyzing results with the Prompt inoculation method by individual species, several species exhibited unacceptable EA performance (i.e., EA <90%) across all read methods with EA ranging from 40.0% to 87.5%. In addition, evaluable EA for these individual species was notably low, ranging from 5% to 50% across all read methods. Taken collectively, these findings indicate a performance concern specific to the Prompt inoculation method when testing Enterobacterales/cefepime. The unacceptable performance with the Prompt inoculation method was addressed with the following limitation in the device labeling:

> *Results obtained with Enterobacterales and cefepime for all read methods with the Prompt inoculation system were outside of essential agreement when compared to the reference method. If critical to patient care, Enterobacterales should be retested using the Turbidity inoculation method.*

A range of MAJ rates were observed for different read and inoculation methods: 0.5% (2/396) to 0.8% (3/396), which were acceptable. One VMJ (1.3%; 1/78) was observed for the WalkAway read method and the Turbidity inoculation method, which was acceptable. The susceptible-dose dependent (SDD) category is treated as an Intermediate (I) category for performance analysis. Device performance was also evaluated by individual species with STIC-recognized breakpoints within the Enterobacterales reporting group. All species that demonstrated acceptable performance, with acceptable mitigations as described below, were included in the indications for use.

When evaluating performance of *C. freundii* complex, one MAJ error was observed with all read methods using the Turbidity inoculation method, resulting in a MAJ rate of 3.9% (1/26), which was not acceptable. This is addressed with the following limitation in the device labeling:

Due to the occurrence of one major error with C. freundii complex and cefepime with Turbidity inoculation and all read methods, MIC results of 32 µg/mL should be confirmed by an alternate method prior to reporting.

For *C. koseri*, insufficient number of resistant isolates were available for evaluation during clinical or challenge testing. This is addressed with the following limitation in the device labeling:

The ability of the MicroScan Dried Gram Negative Panels to detect resistance to cefepime is unknown with C. koseri because an insufficient number of resistant strains were available at the time of comparative testing. Isolates yielding MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory.

When evaluating performance of *M. morganii*, one VMJ error was observed with WalkAway read method using the Turbidity inoculation method, resulting in a VMJ rate of 50.0% (1/2). Due to the limited number of resistant isolates tested with this species, the error was considered random. This is addressed with the following footnote to the Performance Characteristics table in the device labeling:

One very major error (VMJ) was observed with cefepime when testing Morganella morganii with the turbidity inoculation and WalkAway read methods that resulted in an unacceptable VMJ rate (50.0%, 1/2). This was considered random due to the limited number of resistant Morganella morganii isolates tested.

When evaluating performance of *Enterobacter* spp., the CA was not acceptable (< 90%; the EA of evaluable results was also < 90%) across all read methods using the Turbidity inoculation method due to the minor errors. *Enterobacter* spp. performance with cefepime was further evaluated by assessing performance of combined verification and validation data (i.e., clinical study). Data from additional testing of 41 *E. cloacae* complex isolates was combined with cefepime original data, resulting in a total n=95, and evaluated for overall species performance. These combined *Enterobacter* spp. data demonstrate acceptable performance across all read methods using the Turbidity inoculation method.

Pseudomonas aeruginosa

The overall EA and CA performance for *P. aeruginosa* for the WalkAway, autoSCAN-4, and manual read methods were acceptable (> 90%) for all inoculation methods. No MAJ or VMJ errors were observed.

***Aeromonas* spp.**

The overall EA and CA performance for *Aeromonas* spp. using both the Prompt and Turbidity inoculation methods across all read methods (i.e., autoSCAN-4, Manual, and WalkAway read methods) were acceptable (> 90%), with one exception. The combination of the Turbidity inoculation method with the WalkAway read method yielded unacceptable CA (< 90%; the EA of evaluable results was also < 90%). This was primarily due to a VMJ error

(1/6; 16.7%) and minor errors. This is addressed with the following limitation in the device labeling:

> *Performance of cefepime when testing Aeromonas spp. using the Turbidity inoculation method with the WalkAway read method were within essential agreement, but outside of categorical agreement due to the elevated very major error rate and minor errors when compared to the reference method. Aeromonas spp. results with the Turbidity/WalkAway should be read manually prior to reporting.*

Additionally, when evaluating performance of *Aeromonas* spp., the combination of the Turbidity inoculation method with the autoSCAN-4 and Manual read methods yielded CA <90% due to minor errors. However, the EA of evaluable results was 100%. One VMJ error was observed with all read methods using the Prompt inoculation method, resulting in a VMJ rate of 16.7% (1/6), which is not acceptable. Due to the limited number of resistant isolates tested with this species, the error was considered random. These are addressed with the following footnotes to the Performance Characteristics table in the device labeling:

> *Categorical agreement of Aeromonas spp. and cefepime for the autoSCAN-4 and Manual reads with turbidity inoculation was 87.1% (27/31). Aeromonas spp. performance is acceptable due to 100% (8/8) essential agreement of evaluable isolates and all categorical discrepancies were minor errors.*
>
> *One very major error (VMJ) was observed with cefepime when testing Aeromonas spp. with the Prompt inoculation and all read methods that resulted in an unacceptable VMJ rate (16.7%, 1/6). This was considered random due to the limited number of resistant Aeromonas spp. isolates tested.*

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

A trending analysis was conducted using the combined data (clinical and challenge) obtained with each organism group for each inoculation and read method (**Table 5**). This trending calculation analyzes device MIC values that are one or more doubling dilutions lower or higher than the reference method MIC values. MIC values that are off-scale for both the reference and device are not considered in the trending analysis. Organism groups or species for which the difference between the percentage of isolates with higher or lower MIC values

was ≥30% with a statistically significant confidence interval were considered to have evidence of trending and is addressed in device labeling.

Table 5. Trending Observed for Cefepime

Inoculation/ Read Method	Organism Group	Total Evaluable for Trending	≥ 1 Dilution Lower # (%)	Exact # (%)	≥ 1 Dilution Higher # (%)	Percent Difference (95% CI)	Trending Noted
Prompt/ WalkAway	Enterobacterales	135	31, (22.96)	24	80, (59.26)	36%, (25%, 46%)	Yes
	P. aeruginosa	64	14, (21.88)	40	10, (15.62)	-6%, (-20%, 7%)	No
	Aeromonas spp.	11	6, (54.55)	2	3, (27.27)	-27%, (-57%, 12%)	No
Prompt/ autoSCAN-4	Enterobacterales	136	31, (22.79)	23	82, (60.29)	38%, (26%, 48%)	Yes
	P. aeruginosa	64	17, (26.56)	38	9, (14.06)	-12%, (-26%, 2%)	No
	Aeromonas spp.	11	6, (54.55)	2	3, (27.27)	-27%, (-57%, 12%)	No
Prompt/ Manual	Enterobacterales	155	29, (18.71)	23	103, (66.45)	48%, (37%, 57%)	Yes
	P. aeruginosa	64	15, (23.44)	39	10, (15.62)	-8%, (-21%, 6%)	No
	Aeromonas spp.	12	6, (50)	2	4, (33.33)	-17%, (-48%, 20%)	No
Turbidity/ WalkAway	Enterobacterales	111	61, (54.95)	31	19, (17.12)	-38%, (-49%, -26%)	Yes
	P. aeruginosa	64	13, (20.31)	44	7, (10.94)	-9%, (-22%, 3%)	No
	Aeromonas spp.	10	9, (90)	1	0, (0)	-90%, (-98%, -49%)	Yes
Turbidity/ autoSCAN-4	Enterobacterales	111	59, (53.15)	33	19, (17.12)	-36%, (-47%, -24%)	Yes
	P. aeruginosa	64	15, (23.44)	45	4, (6.25)	-17%, (-29%, -5%)	No
	Aeromonas spp.	10	9, (90)	1	0, (0)	-90%, (-98%, -49%)	Yes
Turbidity/ Manual	Enterobacterales	116	59, (50.86)	36	21, (18.1)	-33%, (-43%, -21%)	Yes
	P. aeruginosa	64	13, (20.31)	47	4, (6.25)	-14%, (-26%, -2%)	No
	Aeromonas spp.	10	9, (90)	1	0, (0)	-90%, (-98%, -49%)	Yes

Enterobacterales

The Enterobacterales trending with the Prompt inoculation method is addressed by the limitation in the device labeling that restricts reporting Enterobacterales/cefepime results across all read methods when using the Prompt inoculation method. A bias for lower MIC values was observed for Enterobacterales with all read methods and the Turbidity inoculation method.

P. aeruginosa

No trending was observed for *P. aeruginosa.*

***Aeromonas* spp.**

A bias for lower MIC values was observed for *Aeromonas* spp. with all read methods using the Turbidity inoculation method. The trending for Enterobacterales and *Aeromonas* spp. with all read methods using the Turbidity inoculation method is addressed in the following footnote to the performance table in the device labeling:

> *Cefepime MIC values for Aeromonas spp. and Enterobacterales species were most frequently in exact agreement with the reference method with Turbidity inoculation*

method. When not in agreement results tended to be one or more doubling dilutions lower for Aeromonas spp. and Enterobacterales species for all reads with Turbidity inoculation.

Resistance Mechanism Characterization
Challenge isolates of Enterobacterales and *P. aeruginosa* harboring various molecular mechanisms of resistance were tested with cefepime. Challenge isolates included strains from the CDC and FDA Antibiotic Resistance Isolate Bank for evaluation.

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 6: FDA-Identified and Recognized Interpretive Criteria for Cefepime (µg/mL)

Organisms	Interpretive Criteria[a]			
	S	SDD	I	R
Enterobacterales	≤2	4-8	-	≥16
Pseudomonas aeruginosa	≤8	-	16	≥32
Aeromonas spp.	≤2	-	4-8	≥16

S = Susceptible; SDD = Susceptible-dose dependent; I = Intermediate; R = Resistant
[a] FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria Website https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria

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/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria). The protocol outlined the specific procedures and acceptance criteria that Beckman Coulter, Inc. intends to use to evaluate the MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64 µg/mL) device when revised breakpoints for cefepime are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Beckman Coulter, Inc. will update the MicroScan Dried Gram-Negative MIC/Combo Panels with Cefepime (CPE) (0.12-64 µg/mL) 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.