510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K250084

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

MicroScan Dried Gram-Negative MIC/Combo Panels with Aztreonam (AZT) (0.5-64 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LTT	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology
JWY	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LRG	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LTW	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for aztreonam at concentrations of 0.5-64 µg/mL with the MicroScan Dried Gram-Negative MIC/Combo Panels for susceptibility testing of non-fastidious Gram-negative organisms.

B Measurand:

Aztreonam in the dilution range of 0.5-64 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 aztreonam at concentrations of 0.5-64 µg/mL to the test panel. Testing is indicated for Enterobacterales and Pseudomonas aeruginosa, as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC) webpage.

The MicroScan Dried Gram-Negative MIC/Combo Panels with Aztreonam (AZT) (0.5-64 µg/mL) has demonstrated acceptable performance with the following organisms:

Enterobacterales (*Citrobacter freundii* complex, *Citrobacter koseri*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Morganella morganii*, *Yersinia enterocolitica*)

Pseudomonas aeruginosa

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

Results obtained with the organism/antimicrobial agent combinations listed below 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.
Aztreonam: Enterobacter cloacae complex, Serratia marcescens, Serratia liquefaciens complex, Proteus vulgaris, Providencia stuartii, and Providencia rettgeri.

Performance of aztreonam when testing Citrobacter koseri have shown discrepant MICs (unacceptable essential agreement and an elevated very major error rate) when compared with the reference method across all read methods with the Prompt inoculation system. An alternate testing method (e.g., autoSCAN-4/WalkAway/manual reads with turbidity inoculation) should be used for aztreonam with Citrobacter koseri.

Performance of aztreonam when testing M. morganii and P. mirabilis using the Prompt inoculation method with all read methods was outside of essential agreement with unacceptable major error rates compared to the reference method. M. morganii and P. mirabilis should only be tested with the turbidity inoculation method.

Due to the occurrence of major errors with aztreonam, P. mirabilis isolates with an MIC ≥ 16 µg/mL run on the WalkAway/Turbidity method should be read manually prior to reporting.

Due to the occurrence of a very major error involving a single E. coli isolate tested with aztreonam, isolates with an MIC ≤4 µg/mL run on the autoSCAN-4/Turbidity method should be read manually prior to reporting.

Performance of aztreonam when testing Yersinia enterocolitica using the Prompt inoculation method with the WalkAway read method were within categorical agreement, but outside of essential agreement due to a single isolate when compared to the reference method. Yersinia enterocolitica results with the Prompt/WalkAway should be read manually prior to reporting.

The ability of the MicroScan Dried Gram Negative Panels to detect resistance to aztreonam is unknown with Y. enterocolitica 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 aztreonam 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-CO2 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: K250084	Predicate: K202343
Device Trade Name	MicroScan Dried Gram-Negative MIC/Combo Panels with Aztreonam (Azt) (0.5-64 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 Aztreonam 0.5-64 µg/mL	Dried Ceftazidime 0.5-64 µg/mL

VI Standards/Guidance Documents Referenced:

CLSI M07, 11th ed., "*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard*" (January 2018)

CLSI M100, 35th ed., "*Performance Standards for Antimicrobial Susceptibility Testing*" (January 2025)

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 organisms that were consistent with the device intended use. The range of aztreonam dilutions tested was 0.5-64 µg/mL. Isolates were tested in triplicate over three days at three clinical sites (27 data points per isolate). The isolates tested in the reproducibility study included 4 isolates of *Pseudomonas aeruginosa*, 3 isolates of *Klebsiella aerogenes*, 2 isolates of *Klebsiella oxytoca*, and 1 isolate of *Enterobacter cloacae* complex.

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 was 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 Aztreonam 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	266/270 (98.5)	259/270 (95.5)	270/270 (100)	264/270 (97.8)
autoSCAN-4	265/270 (98.1)	258/270 (95.6)	266/270 (98.5)	256/270 (95.0)
Manual	267/270 (98.9)	262/270 (97.0)	266/270 (98.5)	261/270 (96.7)

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 strains *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853, as well as monthly QC testing with the turbidity inoculation method. 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. 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 organisms *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested with all inoculation and read methods using eight dilutions of aztreonam (0.5 – 64 µg/mL). The reference panel was inoculated using the turbidity method only. In this submission, the QC ranges for *P. aeruginosa* ATCC 27853 reflect the current MIC ranges recommended in the CLSI document M100, *Performance Standards for Antimicrobial Susceptibility Testing* 35th ed. The results of QC testing are shown in **Table 2**. For *P. aeruginosa* ATCC 27853, quality control results were within the acceptable range for all inoculation and read methods for ≥95% of tests which is acceptable. The device does not include the full CLSI/FDA-recommended dilution range for *E. coli* ATCC25922. Results ≤ the lowest dilution on the panel (i.e., ≤0.5 µg/mL) were considered an acceptable result and ≥95% of tests were in that range for all inoculation and read methods.

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

Organism	Conc. (µg/mL) [1]	Reference [2]	Prompt Inoculation Method			Turbidity Inoculation Method		
			autoSCAN-4	Manual	WalkAway	autoSCAN-4	Manual	WalkAway
E. coli ATCC 25922 Expected Range 0.06-0.5 µg/mL	≤ 0.5	186	179	180	180	183	184	185
	1	1	5	3	4	1	2	1
	2		2	3	2	1		1
	4		1					
	8			1		1	1	1
	16							
	32				1	2	2	2
	64	2						
	> 64							
P. aeruginosa ATCC 27853 Expected Range 2-8 µg/mL	≤ 0.5							
	1							
	2	2	117	113	89	123	114	87
	4	162	60	67	75	48	59	80
	8	24	11	8	18	11	13	16
	16				7	2		2
	32					1		1
	64	1						
	> 64							

[1] Does not include the full CLSI/FDA-recommended dilution range for QC testing of *E. coli* ATCC 25922 with the reference panel or the MicroScan panel. For *E. coli* ATCC25922, an acceptable result will be ≤ the lowest dilution on the panel (i.e., ≤0.5 µg/mL)

[2] 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 Panel with Aztreonam (Azt) (0.5-64 µg/mL) were compared to results obtained using a frozen broth microdilution reference panel (dilution range 0.5-64 µg/mL). Clinical isolates were evaluated at three testing sites in the U.S.; challenge isolates were evaluated at one internal and one external clinical 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 16-18 hours.

Clinical Study
To determine the performance of MicroScan Dried Gram-Negative MIC/Combo Panel with Aztreonam, a total of 622 gram-negative clinical isolates were evaluated with the Prompt inoculation method and the Turbidity inoculation method and all read methods at three clinical sites. Isolates included *Pseudomonas aeruginosa* (94 isolates) and Enterobacterales (528 isolates including 3 isolates of *Citrobacter amalonaticus,* 15 isolates of *Citrobacter fruendii*, 3 isolates of *Citrobacter koseri*, 41 isolates of *Enterobacter cloacae*, 1 isolates of *Enterobacter gergoviae*, 214 isolates of *Escherichia coli*, 1 isolates of *Hafnia alvei*, 17 isolates of *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*), 14 isolates of *Klebsiella oxytoca*, 71 isolates of *Klebsiella pneumoniae*, 1 isolate of *Klebsiella* spp., 16 isolates of *Morganella morganii*, 1 isolate of *pantoea agglomerans*, 89 isolates of *Proteus mirabilis*, 1 isolate of *Proteus penneri*, 2 isolates of *Proteus vulgaris*, 1 isolate of *Providencia rettgeri*, 3 isolates of *Providencia stuartii*, and 34 isolates of *Serratia marcescens*).

Performance when testing *Enterobacter cloacae* complex*, Serratia marcescens, Serratia liquefaciens complex, Proteus vulgaris, Providencia stuartii, and Providencia rettgeri* was not acceptable. These species were excluded from the intended use of the MicroScan Dried Gram-Negative MIC/Combo Panel with Aztreonam leaving a total of 540 clinical isolates (446 Enterobacterales and 94 *P. aeruginosa*) in the performance evaluation. This is addressed with the following limitation in the device labeling:

> *Results obtained with the organism/antimicrobial agent combinations listed below 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.*
>
> *Aztreonam: Enterobacter cloacae complex, Serratia marcescens, Serratia liquefaciens complex, Proteus vulgaris, Providencia stuartii, and Providencia rettgeri*

Of the 540 clinical isolates (446 Enterobacterales and 94 *P. aeruginosa*) with results included in the performance analysis, a total of 471 (87.2%) were fresh isolates, and 69 (12.7%) were stock isolates (isolated from clinical specimens and tested beyond six months of isolation).

Challenge Study
A total of 148 gram-negative challenge isolates were evaluated at two sites including *Psuedomonas aeruginosa* (21 isolates) and Enterobacterales (127 isolates including 6 isolates

of *Citrobacter fruendii*, 3 isolates of *Citrobacter koseri*, 5 isolates of *Enterobacter cloacae*, 21 isolates of *Escherichia coli*, 11 isolates of *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*), 6 isolates of *Klebsiella oxytoca*, 11 isolates of *Klebsiella pneumoniae*, 14 isolates of *Morganella morganii*, 6 isolates of *Proteus mirabilis*, 6 isolates of *Proteus vulgaris*, 8 isolates of *Providencia rettgeri*, 8 isolates of *Providencia stuartii*, 4 isolates of *Serratia liquerfaciens*, 9 isolates of *Serratia marcescens*, and 9 isolates of *Yersenia enterocolitica*). Results obtained with *Enterobacter* spp., *Serratia* spp., *Proteus vulgaris, Providencia stuartii,* and *Providencia rettgeri* were removed from the device indications for use and were not included in analysis, leaving a total of 108 challenge isolates (87 Enterobacterales and 21 *P. aeruginosa* isolates) in the performance evaluation. One isolate of *P. aeruginosa* was not assessed in the Prompt inoculation method due to colony mucoid morphology leaving only 20 isolates for this evaluation.

Results for essential agreement, category agreement, and categorical errors for Enterobacterales and *Pseudomonas aeruginosa* for all inoculation and read methods are shown in **Table 3** and **Table 4**. 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 and *P. aeruginosa*) due to differences in susceptibility test interpretive criteria.

For *Y. enterocolitica*, no 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 aztreonam is unknown with Y. enterocolitica 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.*

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

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R/NS	No. S/SDD	min	maj	vmj
autoSCAN-4 Read													
***Overall Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)*													
Clinical	446	422	94.6	57	33	57.9	428	96.0	46	392	10	8	0
Challenge	87	73	83.9	50	36	72	74	85.1	47	37	9	2	2
Combined	533	495	92.9	107	69	64.5	502	94.2	93	429	19	10	2
***Pseudomonas aeruginosa*, ≤8 (S), 16 (I), ≥32 (R)**													
Clinical	94	89	94.7	83	78	94.0	88	93.6	14	70	6	0	0
Challenge	20	19	95.0	20	19	95	12	60.0	8	4	8	0	0
Combined	114	108	94.7	103	97	94.2	100	87.7	22	74	14	0	0
Manual Read													
***Overall Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)*													
Clinical	446	422	94.6	57	33	57.9	426	95.5	46	392	11	9	0
Challenge	87	73	83.9	51	37	72.6	74	85.1	47	37	9	2	2
Combined	533	495	92.9	108	70	64.8	500	93.8	93	429	20	11	2
***Pseudomonas aeruginosa*, ≤8 (S), 16 (I), ≥32 (R)**													
Clinical	94	90	95.7	84	80	95.2	86	91.5	14	70	7	1	0

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R/NS	No. S/SDD	min	maj	vmj
Challenge	20	19	95.0	20	19	95	12	60.0	8	4	8	0	0
Combined	114	109	95.6	104	99	95.2	98	86.0	22	74	15	1	0
WalkAway Read													
***Overall Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)*													
Clinical	446	416	93.3	63	33	52.4	424	95.1	46	392	10	12	0
Challenge	87	69	79.3	52	34	65.4	72	82.8	47	37	9	4	2
Combined	533	485	91.0	115	67	58.3	496	93.1	93	429	19	16	2
***Pseudomonas aeruginosa*, ≤8 (S), 16 (I), ≥32 (R)**													
Clinical	94	87	92.6	83	76	91.6	83	88.3	14	70	9	2	0
Challenge	20	17	85.0	20	17	85	15	75.0	8	4	5	0	0
Combined	114	104	91.2	103	93	90.3	98	86.0	22	74	14	2	0

*Includes 6.4% (34/533) of non-indicated Enterobacterales

EA – Essential agreement
CA – Category agreement
EVAL – Evaluable isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies
S – Susceptible
SDD – Susceptible-Dose Dependent
R – Resistant

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 Aztreonam, Using *Turbidity* Inoculation and all Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R/NS	No. S/SDD	min	maj	vmj
autoSCAN-4 Read													
***Overall Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)*													
Clinical	446	436	97.8	47	37	78.7	432	96.9	46	392	9	4	1
Challenge	87	80	92.0	49	42	85.7	77	88.5	47	37	9	0	1
Combined	533	516	96.8	96	79	82.3	509	95.5	93	429	18	4	2
***Pseudomonas aeruginosa*, ≤8 (S), 16 (I), ≥32 (R)**													
Clinical	94	92	97.9	83	81	97.6	87	92.6	14	70	7	0	0
Challenge	21	21	100	20	20	100	12	57.1	9	4	9	0	0
Combined	115	113	98.3	103	101	98.1	99	86.1	23	74	16	0	0
Manual Read													
***Overall Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)*													
Clinical	446	435	97.5	48	37	77.1	432	96.9	46	392	10	4	0
Challenge	87	81	93.1	50	44	88.0	76	87.4	47	37	10	0	1
Combined	533	516	96.8	98	81	82.7	508	95.3	93	429	20	4	1
***Pseudomonas aeruginosa*, ≤8 (S), 16 (I), ≥32 (R)**													
Clinical	94	91	96.8	84	81	96.43	86	91.5	14	70	7	1	0
Challenge	21	21	100	20	20	100	12	57.1	9	4	9	0	0
Combined	115	112	97.4	104	101	97.12	98	85.2	23	74	16	1	0
WalkAway Read													
***Overall Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)*													
Clinical	446	436	97.8	48	38	79.2	431	96.7	46	392	10	5	0
Challenge	87	80	92.0	52	45	86.5	77	88.5	47	37	9	0	1
Combined	533	516	96.8	100	83	83.0	508	95.3	93	429	19	5	1
***Pseudomonas aeruginosa*, ≤8 (S), 16 (I), ≥32 (R)**													
Clinical	94	90	95.7	84	80	95.24	86	91.5	14	70	6	2	0
Challenge	21	21	100	20	20	100	15	71.4	9	4	6	0	0

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R/NS	No. S/SDD	min	maj	vmj
Combined	115	111	96.5	104	100	96.15	101	87.8	23	74	12	2	0

*Includes 6.4% (34/533) of non-indicated Enterobacterales

EA – Essential agreement
CA – Category agreement
EVAL – Evaluable isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies
S – Susceptible
SDD – Susceptible-Dose Dependent
R – Resistant

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.

The overall EA and CA performance for Enterobacterales for the WalkAway, autoSCAN-4, and manual read methods were acceptable (> 90%) for each inoculation method. A range of MAJ rates were observed for the different read and inoculation methods: 0.9% (4/429) to 3.7% (16/429), which is not acceptable. A range of VMJ rates were observed for the different read and inoculation methods: 1.1% (1/93) to 2.1% (2/93), which is acceptable. The unacceptable MAJ error rate observed for Enterobacterales is addressed by the limitations described below.

When the performance for Enterobacterales was evaluated individually by species, the following performance issues were observed:

When evaluating performance of *E.* coli, the overall EA and CA performance for *E. coli* for the WalkAway, autoSCAN-4, and manual read methods were acceptable with the prompt and turbidity inoculation methods. One very major error was observed, resulting in a VMJ rate of 3.2% (1/31), which was unacceptable. This is addressed with the following limitation in the device labeling:

Due to the occurrence of a very major error involving a single E. coli isolate tested with aztreonam, isolates with an MIC ≤4 µg/mL run on the autoSCAN-4/Turbidity method should be read manually prior to reporting.

When evaluating performance of *P. mirabilis,* the overall EA and CA performance for the manual read method was acceptable for the prompt inoculation method. The overall EA and CA performance for *P. mirabilis* for the WalkAway, AutoSCAN-4, and manual read methods were acceptable with the turbidity inoculation method. However, four major errors were observed with the AutoSCAN-4 read method resulting in a MAJ rate of 4.4% (4/92), six major errors were observed with the manual read method resulting in a MAJ rate of 6.5% (6/92), and eight major errors were observed with the WalkAway read method resulting in a MAJ rate of 8.7% (8/92) all using the prompt inoculation method, which was unacceptable. In addition, three major errors were observed with the WalkAway and turbidity inoculation method resulting in a MAJ rate of 3.3% (3/92), which is not acceptable. This is addressed with the following limitations in the device labeling:

Performance of aztreonam when testing M. morganii and P. mirabilis using the Prompt inoculation method with all read methods was outside of essential agreement with

unacceptable major error rates compared to the reference method. M. morganii and P. mirabilis should only be tested with the turbidity inoculation method.

Due to the occurrence of major errors with aztreonam, P. mirabilis isolates with an MIC ≥ 16 µg/mL run on the WalkAway/Turbidity method should be read manually prior to reporting.

When evaluating performance of *M. morgannii*, the overall EA and CA performance for the WalkAway, AutoSCAN-4, and manual read methods were acceptable with the turbidity inoculation method. One major error was observed with the AutoSCAN-4 read method and manual read method resulting in a MAJ rate of 5.9% (1/17), and two major errors were observed with the WalkAway read method all using the prompt inoculation method resulting in a MAJ rate of 11.8% (2/17) which is not acceptable. This is addressed with a limitation in the device labeling (described above) to only test *M. morganii* with the turbidity inoculation method.

When evaluating performance of *Citrobacter koseri*, one very major error was observed with all read methods for the prompt inoculation method which resulted in a VMJ rate of 11.1% (1/9), which is not acceptable. This is addressed with the following limitation in the device labeling:

Performance of aztreonam when testing Citrobacter koseri have shown discrepant MICs (unacceptable essential agreement and an elevated very major error rate) when compared with the reference method across all read methods with the Prompt inoculation system. An alternate testing method (e.g., autoSCAN-4/WalkAway/manual reads with turbidity inoculation) should be used for aztreonam with Citrobacter koseri.

When evaluating performance of *Citrobacter freundii* complex, one very major error was observed with all read and inoculation methods resulting in a VMJ rate of 11.1% (1/9), which is not acceptable. This is addressed with the following footnote to the Performance Characteristics table in the device labeling:

For aztreonam, one resistant strain of Citrobacter freundii complex had a single very major error compared to the reference method across all read methods with turbidity inoculation.

When evaluating performance of *Y. enterocolitica*, one isolate was outside of essential agreement for the WalkAway read and Prompt inoculation method resulting in a EA rate of 88.9% (8/9), which is not acceptable. This is addressed with the following limitation in the device labeling:

Performance of aztreonam when testing Yersinia enterocolitica using the Prompt inoculation method with the WalkAway read method were within categorical agreement, but outside of essential agreement due to a single isolate when compared to the reference method. Yersinia enterocolitica results with the Prompt/WalkAway should be read manually prior to reporting.

The overall EA for *P. aeruginosa* for the WalkAway, autoSCAN-4, and manual read methods were acceptable (>90%) for both inoculation methods. In addition, a range of MAJ

rates was observed with all read methods when using the Prompt inoculation method: 0% (0/74) to 2.7% (2/74), which is acceptable. A range of MAJ rates was observed with all read methods when using the turbidity inoculation method: 0% (0/74) to 2.7% (2/74), which is acceptable. However, the CA was not acceptable across all read and inoculation methods. After further analysis, this was considered acceptable due to the acceptable performance of the evaluable isolates and the majority of the errors being minor. This is addressed with the following footnote to the Performance Characteristics table in the device labeling:

> *Categorical agreement for P. aeruginosa and aztreonam ranged from 85.2% (98/115) – 87.8% (101/115) across all read and inoculation methods. Pseudomonas aeruginosa performance is acceptable due to the essential agreement of evaluable isolates ranging from 90.3% (93/103) – 95.2% (99/104) and the majority of the categorical discrepancies were minor errors.*

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 (Enterobacterales and *P. aeruginosa*) and for each inoculation and read method (**Table 5**). This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions 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.

Species 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 shows higher or lower MIC values compared to the reference is addressed in the labeling.

No trending was observed for Enterobacterales or *P. aeruginosa* organism groups with all inoculation and read methods. At a species level, a trend toward higher MIC values was observed for *P. mirabilis* across both inoculation methods and all read methods. A trend toward lower MIC values was observed for *K. oxytoca* (turbidity inoculation/all read methods and Prompt inoculation/manual read method), *M. morganii* (turbidity inoculation/all read methods), and *Y. enterocolitica* (turbidity inoculation/autoSCAN-4 read method and turbidity inoculation/manual read method).

To address the MIC trending, the sponsor included the following footnote to the Performance Characteristics table in the device labeling:

Aztreonam MIC values for Enterobacterales were most frequently in exact agreement with the reference method. When not in agreement results tended to be one or more doubling dilutions higher for P. mirabilis with all read/all inoculation methods. When not in agreement results tended to be one doubling dilution lower for K. oxytoca and M. morganii with all read methods/turbidity inoculation, Y. enterocolitica with the autoSCAN-4/manual read methods/turbidity inoculation and K. oxytoca with the manual read /Prompt inoculation.

Table 5. Trending Observed for Aztreonam

Inoculation/ Read Method	Organism Group	Total Evaluable for Trending	≥ 1 Dilution Lower # (%)	Exact # (%)	≥ 1 Dilution Higher # (%)	Percent Difference (95% CI)	Trending Noted
Prompt/ autoSCAN-4	Overall *Enterobacterales*	130	47, (36.2)	27 (20.7)	56, (43.1)	7%, (-5 to 18)	No
	Pseudomonas aeruginosa	107	39, (36.4)	60 (56.1)	8, (7.5)	-29%, (-39 to -18)	No
Prompt/ Manual	Overall *Enterobacterales*	126	45, (35.7)	30 (23.8)	51, (40.5)	5%, (-7 to 16)	No
	Pseudomonas aeruginosa	106	30, (28.3)	62 (58.7)	14, (13.2)	-15%, (-26, -4)	No
Prompt/ WalkAway	Overall *Enterobacterales*	135	43, (31.9)	29 (21.4)	63, (46.7)	15%, (3 to 26)	No
	Pseudomonas aeruginosa	105	19, (18.1)	65 (x)	21, (20.0)	2%, (-9 to 13)	No
Turbidity/ autoSCAN-4	Overall *Enterobacterales*	112	59, (52.7)	26 (x)	27, (24.1)	-29%, (-40 to -16)	No
	Pseudomonas aeruginosa	106	42, (39.6)	53 (x)	11, (10.4)	-29%, (-40 to 18)	No
Turbidity/ Manual	Overall *Enterobacterales*	112	55, (49.1)	28 (x)	29, (25.9)	-23%, (-35 to -11)	No
	Pseudomonas aeruginosa	107	39, (36.5)	55 (x)	13, (12.2)	-24%, (-35 to -13)	No
Turbidity/ WalkAway	Overall *Enterobacterales*	115	56, (48.7)	30 (x)	29, (25.2)	-23%, (-35 to -11)	No
	Pseudomonas aeruginosa	106	30, (28.3)	60 (x)	16, (15.1)	-13%, (-24 to -2)	No

Resistance Mechanism Characterization
Challenge isolates of Enterobacterales and *P. aeruginosa* harboring various molecular mechanisms of resistance were tested with aztreonam. 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 Aztreonam (µg/mL)

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

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 Aztreonam (AZT) (0.5-64 µg/mL) device when revised breakpoints for aztreonam 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 Aztreonam (AZT) (0.5-64 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.