510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K202343

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

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

D Regulatory Information

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

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for ceftazidime 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:

Ceftazidime 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):

MicroScan Dried Gram Negative MIC/Combo Panels are designed for use in determining quantitative and/or qualitative antimicrobial susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative Gram-negative bacilli.

B Indication(s) for Use:

The MicroScan Dried Gram-Negative MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram-negative bacilli. After inoculation, panels are incubated for 16 – 20 hours at 35°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 updated susceptibility test interpretative criteria for *Enterobacterales, Pseudomonas aeruginosa* and *Acinetobacter* spp. for the antimicrobial ceftazidime (Caz) at concentrations of 0.5 to 64 µg/mL to the test panel.

Ceftazidime has been shown to be active *in vitro* against most strains of microorganisms listed below, as described in the FDA-approved package insert for this antimicrobial agent.

Active *in vitro* and in clinical infections against:
Citrobacter species
Enterobacter species
Escherichia coli
Klebsiella species
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia species

Active *in vitro* but clinical significance is unknown:
Acinetobacter species
Citrobacter koseri (formerly *Citrobacter diversus*)
Citrobacter freundii
Salmonella species
Shigella species
Yersinia enterocolitica

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. If the antimicrobial agent is critical to patient care, an alternate procedure should be used.

  Ceftazidime: *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia, Providencia* spp. and *Morganella morganii*

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

- Results obtained with *Enterobacter* spp. and ceftazidime for all read methods with the Prompt inoculation system and manual reads with turbidity inoculation were within categorical agreement, but outside of essential agreement when compared to the reference method. If critical to patient care, *Enterobacter* spp. isolates should be retested using an alternate method.

- Results obtained with *Proteus vulgaris* and ceftazidime for the WalkAway and Manual read methods with both the Prompt and turbidity inoculation methods were within categorical agreement, but outside of essential agreement when compared to the reference method. If critical to patient care, *Proteus vulgaris* isolates should be retested using an alternate method.

- Performance of ceftazidime when testing *Serratia* species using the Prompt inoculation method with the WalkAway, autoSCAN-4 or manual read methods were outside of essential agreement and categorical agreement compared to the reference method. *Serratia* species should only be tested using the turbidity inoculation method.

- Due to the occurrence of very major errors with *Klebsiella* spp. and ceftazidime with the autoSCAN-4 read with turbidity inoculation, MIC results of 2 or 4 μg/mL should be confirmed by manual read prior to reporting.

D Special Instrument Requirements:

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

IV Device/System Characteristics:

A Device Description:

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

B Predicate 510(k) Number(s):
K193536

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K202343	Predicate: K193536
Device Trade Name	MicroScan Dried Gram-Negative MIC/Combo Panels with Ceftazidime (Caz) (0.5-64 µg/mL)	MicroScan Dried Gram Negative MIC/Combo Panels with Ciprofloxacin (Cp) (0.004 – 8 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 Ceftazidime 0.5 – 64 µg/mL	Dried Ciprofloxacin 0.004 – 8 µg/mL

VI Standards/Guidance Documents Referenced:

- Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.
- CLSI M07, 10th ed., "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard, January 2015".
- CLSI M100, 30th ed., "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Ninth Informational Supplement, January 2020".

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study was conducted at four clinical sites using 10 isolates of Gram-negative bacilli that were consistent with the intended use. The range of ceftazidime dilutions tested was 0.5 – 64 µg/mL. Isolates were tested in triplicate over three days at three of the four clinical sites (27 data points per isolate). The quality control strain was out of range on one testing day which excluded data from that day, resulting in 267 total data points. The isolates tested in the reproducibility study included: *A. baumannii* (1 isolate), *E. coli* (2 isolates), *K. oxytoca* (1 isolate), *K. pneumoniae* (1 isolate), and *P. aeruginosa* (5 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 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 Ceftazidime 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	263/267 (98.5)	263/267 (98.5)	261/267 (97.8)	261/267 (97.8)
autoSCAN-4	264/267 (98.9)	264/267 (98.9)	258/267 (96.6)	258/267 (96.6)
Manual	263/267 (98.5)	263/267 (98.5)	260/267 (97.4)	260/267 (97.4)

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, was 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, one isolate 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 8 dilutions of ceftazidime (0.5 – 64 µg/mL). The reference panel was inoculated using the turbidity method only. In this submission, the QC range for both *E. coli* ATCC 25922 and *P. aeruginosa* reflect the current MIC ranges recommended in the CLSI document M100, *Performance Standards for Antimicrobial Susceptibility Testing* 30th ed. Results of QC testing are shown in **Table 2**. For both QC strains, 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 Ceftazidime

Organism	Conc. (µg/mL) [1]	Reference [2]	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
E. coli ATCC 25922	≤ 0.5	365	371	366	369	363	364	361
	1		3	5	4	1	1	1
	2		1	1	1			

Organism	Conc. (µg/mL) [1]	Reference [2]	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
Expected Range 0.06-0.5 µg/mL	4							
	8					1	1	1
	16		1	1	1			
	32					1	1	1
	64	1	1	1	1			
	> 64							
P. aeruginosa ATCC 27853 Expected Range 1 – 4 µg/mL	≤ 0.5				6			9
	1	299	320	301	322	315	303	312
	2	57	42	46	27	35	44	24
	4	10	12	22	17	10	11	12
	8		3	5	4	4	5	3
	16							
	32							
	64							
	> 64		1	1	1			

[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*, an in-range 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.

AS4: autoSCAN-4

6. Detection Limit:

   Not applicable

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with Reference Method:

   The results obtained with the MicroScan Dried Gram-Negative MIC/Combo Panel with Ceftazidime (dilution range 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 in two studies at four testing sites in the U.S.; challenge isolates were evaluated in three separate studies performed at an internal and two external sites.

   The reference panel was prepared as described in CLSI document M07-A10 (as well as M07-A9 and M07-A8; each of which were effective at various points in the clinical trial), except for the use of Pluronic-F (wetting agent) in the inoculum water for the reference panel. A summary of historical data from eight 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 (20-24 hours for *Acinetobacter* spp.); 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 the MicroScan Dried Gram-Negative MIC/Combo Panel with Ceftazidime, a total of 1373 Gram-negative clinical isolates [*Acinetobacter* spp. (74 isolates), *B. cepacia* complex (8 isolates), *Enterobacterales* (1082 isolates), *P. aeruginosa* (161 isolates), and *S. maltophilia* (48 isolates)] were evaluated with all inoculation and read methods at four sites. The *Enterobacterales* isolates tested include the following indicated species: *C. freundii* (40 isolates), *C. koseri* (47 isolates), *Citrobacter* spp. (10 isolates), *Enterobacter* spp. (87 isolates), *E. coli* (283 isolates), *Klebsiella* spp. (260 isolates), *M. morganii* (52 isolates), *P. mirabilis* (142 isolates), *P. vulgaris* (16 isolates), *P. vulgaris/penneri* (1 isolate), *Providencia* spp. (42 isolates), *Salmonella* spp. (19 isolates), *Serratia* spp. (66 isolates), *Shigella* spp. (2 isolates). An additional 15 isolates of non-indicated *Enterobacterales* species (1.1% of the total number of clinical isolates tested) were also tested and included in the performance evaluation.

Performance when testing *B. cepacia* complex, *S. maltophilia, Providencia* spp. and *M. morganii* was not acceptable. These species were excluded from the intended use for the MicroScan Dried Gram-Negative MIC/Combo Panel with Ceftazidime. As such, 1223 clinical results were included in the performance evaluation. The following limitation for reporting results with these organisms is included 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. If the antimicrobial agent is critical to patient care, an alternate procedure should be used.*
>
> *Ceftazidime: Burkholderia cepacia complex, Stenotrophomonas maltophilia, Providencia spp. and Morganella morganii*

Of the 1223 clinical isolates with results included in the performance analysis, 950 (77.7%) were fresh isolates tested within one week of isolation, 152 (12.4%) were recent/contemporary isolates (isolated from clinical specimens and tested within six months of isolation with minimal sub-culturing), and 121 (9.9%) were stock isolates.

Challenge Study

A total of 128 Gram-negative challenge isolates [*Acinetobacter* spp. (13 isolates), *Enterobacterales* (92 isolates), and *P. aeruginosa* (23 isolates)] were evaluated at two sites. All *Enterobacterales* isolates were indicated species on the FDA-approved drug label which included the following: *C. freundii* (5 isolates), *C. koseri* (2 isolates), *Enterobacter* spp. (5 isolates), *E. coli* (26 isolates), *Klebsiella* spp. (27 isolates), *P. mirabilis* (1 isolate), *P. vulgaris* (3 isolates), *Salmonella* spp. (6 isolates), *Serratia* spp. (9 isolates), *Shigella* spp. (1 isolate), *Y. enterocolitica* group (7 isolates).

Results for essential agreement, categorical agreement, and categorical errors for *Acinetobacter, Enterobacterales* and *P. aeruginosa* 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., *Acinetobacter, Enterobacterales* and *P. aeruginosa*) due to differences in susceptibility test interpretive criteria.

For *P. vulgaris, Shigella* spp., *Salmonella* spp., *Serratia* spp. *and Y. enterocolitica,* no resistant isolates were available for evaluation during clinical or challenge testing. The sponsor included the following limitation in the device labeling:

> *The ability of the MicroScan Dried Gram Negative Panels to detect resistance to ceftazidime is unknown for the following species because an insufficient number of resistant strains were available at the time of comparative testing: P. vulgaris, Shigella spp., Salmonella spp., Serratia spp. and Y. enterocolitica. 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 Ceftazidime, Using *Prompt* Inoculation and all Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
WalkAway Read													
***Acinetobacter* spp., ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	74	69	93.2	42	37	88.1	71	95.9	39	34	2	0	1
Challenge	13	12	92.3	2	1	50.0	11	84.6	11	2	1	1	0
Combined	87	81	93.1	44	38	86.4	82	94.3	50	36	3	1	1
***Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)**													
Clinical	988	915	92.6	159	86	54.1	947	95.9	124	852	23	16	2
Challenge	92	80	87.0	49	37	75.5	81	88.0	41	44	7	3	1
Combined	1080	995	92.1	208	123	59.1	1028	95.2	165	896	30	19	3
***Pseudomonas aeruginosa*, ≤ 8 (S), ≥16 (R)**													
Clinical	161	146	90.7	147	132	89.8	155	96.3	21	140	N/A	6	0
Challenge	23	22	95.7	21	20	95.2	22	95.7	12	11	N/A	1	0
Combined	184	168	91.3	168	152	90.5	177	96.2	33	151	N/A	7	0
autoSCAN-4 Read													
***Acinetobacter* spp., ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	74	71	95.9	42	39	92.9	71	95.9	39	34	2	0	1
Challenge	13	12	92.3	2	1	50.0	11	84.6	11	2	1	1	0
Combined	87	83	95.4	44	40	90.9	82	94.3	50	36	3	1	1
***Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)**													
Clinical	988	948	96.0	125	85	68.0	964	97.6	124	852	16	6	2
Challenge	92	83	90.2	46	37	80.4	82	89.1	41	44	7	2	1
Combined	1080	1031	95.5	171	122	71.3	1046	96.9	165	896	23	8	3
***Pseudomonas aeruginosa*, ≤ 8 (S), ≥16 (R)**													
Clinical	161	150	93.2	147	136	92.5	158	98.1	21	140	N/A	2	1

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
Challenge	23	23	100	23	23	100	22	95.7	12	11	N/A	1	0
Combined	184	173	94.0	170	159	93.5	180	97.8	33	151	N/A	3	1
Manual Read													
***Acinetobacter* spp., ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	74	72	97.3	42	40	95.2	71	95.9	39	34	2	0	1
Challenge	13	12	92.3	3	2	66.7	11	84.6	11	2	1	1	0
Combined	87	84	96.6	45	42	93.3	82	94.3	50	36	3	1	1
***Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)**													
Clinical	988	926	93.7	146	84	57.5	962	97.4	124	852	16	8	2
Challenge	92	84	91.3	44	36	81.8	83	90.2	41	44	6	2	1
Combined	1080	1010	93.5	190	120	63.2	1045	96.8	165	896	22	10	3
***Pseudomonas aeruginosa*, ≤ 8 (S), ≥16 (R)**													
Clinical	161	149	92.5	147	135	91.8	157	97.5	21	140	N/A	4	0
Challenge	23	23	100	23	23	100	22	95.7	12	11	N/A	1	0
Combined	184	172	93.5	170	158	92.9	179	97.3	33	151	N/A	5	0

*Includes non-indicated species (15/1373, 1.1%)

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

N/A – Not applicable due to the lack of an intermediate interpretive criterion for ceftazidime with *P. aeruginosa*
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 Ceftazidime, Using *Turbidity* Inoculation and all Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
WalkAway Read													
***Acinetobacter* spp., ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	74	71	95.9	42	39	92.9	71	95.9	39	34	2	0	1
Challenge	13	13	100	2	2	100	13	100	11	2	0	0	0
Combined	87	84	96.6	44	41	93.2	84	96.6	50	36	2	0	1
***Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)**													
Clinical	988	956	96.8	125	93	74.4	965	97.7	124	852	16	5	2
Challenge	92	87	94.6	43	38	88.4	86	93.5	41	44	4	1	1
Combined	1080	1043	96.6	168	131	78.0	1051	97.3	165	896	20	6	3
***Pseudomonas aeruginosa*, ≤ 8 (S), ≥16 (R)**													
Clinical	161	154	95.7	148	141	95.3	157	97.5	21	140	N/A	3	1
Challenge	23	23	100	23	23	100	22	95.7	12	11	N/A	1	0
Combined	184	177	96.2	171	164	95.9	179	97.3	33	151	N/A	4	1

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
autoSCAN-4 Read													
***Acinetobacter* spp., ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	74	72	97.3	42	40	95.2	71	95.9	39	34	2	0	1
Challenge	13	13	100	3	3	100	13	100	11	2	0	0	0
Combined	87	85	97.7	45	43	95.6	84	96.6	50	36	2	0	1
***Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)**													
Clinical	988	964	97.6	117	93	79.5	970	98.2	124	852	12	3	3
Challenge	92	87	94.6	42	37	88.1	86	93.5	41	44	5	0	1
Combined	1080	1051	97.3	159	130	81.8	1056	97.8	165	896	17	3	4
***Pseudomonas aeruginosa*, ≤ 8 (S), ≥16 (R)**													
Clinical	161	152	94.4	145	136	93.8	157	97.5	21	140	N/A	3	1
Challenge	23	23	100	23	23	100	23	100	12	11	N/A	0	0
Combined	184	175	95.1	168	159	94.6	180	97.8	33	151	N/A	3	1
Manual Read													
***Acinetobacter* spp., ≤ 8 (S), 16 (I), ≥32 (R)**													
Clinical	74	71	95.9	42	39	92.9	71	95.9	39	34	2	0	1
Challenge	13	13	100	3	3	100	13	100	11	2	0	0	0
Combined	87	84	96.6	45	42	93.3	84	96.6	50	36	2	0	1
***Enterobacterales**, ≤4 (S), 8 (I), ≥16 (R)**													
Clinical	988	956	96.8	125	93	74.4	972	98.4	124	852	10	4	2
Challenge	92	87	94.6	43	38	88.4	85	92.4	41	44	6	0	1
Combined	1080	1043	96.6	168	131	78.0	1057	97.9	165	896	16	4	3
***Pseudomonas aeruginosa*, ≤ 8 (S), ≥16 (R)**													
Clinical	161	153	95.0	146	138	94.5	156	96.9	21	140	N/A	3	2
Challenge	23	23	100	23	23	100	22	95.7	12	11	N/A	1	0
Combined	184	176	95.7	169	161	87.5	178	96.7	33	151	N/A	4	2

*Includes non-indicated species (15/1373, 1.1%)

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

N/A – Not applicable due to the lack of an intermediate interpretive criterion for ceftazidime with *P. aeruginosa*

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 *Acinetobacter* spp. for the WalkAway, autoSCAN-4, and manual read methods were acceptable (> 90%) for each inoculation method. One major error (MAJ) was observed for each read method using the prompt inoculation method resulting in MAJ rate of 2.7% (1/36) which is acceptable. One very major error (VMJ) was observed for each read and inoculation method resulting in a VMJ rate of 2.0% (1/50) which is acceptable.

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: 0.3% (3/896) to 2.1% (19/896), which are acceptable. Three VMJs were observed for each read and inoculation method, except the autoSCAN-4 read method using the turbidity inoculation method, resulting in a VMJ rate of 1.8% (3/165), which is acceptable. The autoSCAN-4 read method using the turbidity inoculation method generated a fourth VMJ resulting in a VMJ rate of 2.4% (4/165), which is acceptable.

When the performance for *Enterobacterales* was evaluated individually by species, it was noted the essential agreement was not acceptable (< 90%) for the following species and inoculation/read methods: *Enterobacter* spp. across all read methods using the prompt inoculation method and the manual read method using the turbidity, *Proteus vulgaris* with the WalkAway and Manual read methods using both inoculation methods, and *Serratia* spp. with all read methods using the Prompt inoculation method. This is addressed in the following limitations in the device labeling:

> *Results obtained with Enterobacter spp. and ceftazidime for all read methods with the Prompt inoculation system and manual reads with turbidity inoculation were within categorical agreement, but outside of essential agreement when compared to the reference method. If critical to patient care, Enterobacter spp. isolates should be retested using an alternate method.*
>
> *Results obtained with Proteus vulgaris and ceftazidime for the WalkAway and Manual read methods with both the Prompt and turbidity inoculation methods were within categorical agreement, but outside of essential agreement when compared to the reference method. If critical to patient care, Proteus vulgaris isolates should be retested using an alternate method.*
>
> *Performance of ceftazidime when testing Serratia species using the Prompt Inoculation system with the WalkAway, autoSCAN-4 or manual read methods were outside of essential agreement and categorical agreement compared to the reference method and shall only be tested using the turbidity inoculation method.*

When evaluating performance of *C. freundii* complex, one very major error was observed with all read and inoculation methods, resulting in a VMJ rate of 7.1% (1/14), which is not acceptable. This is addressed with the following footnote to the Performance Characteristics table in the device labeling:

> *One C. freundii complex strain resulted in a very major error with ceftazidime when compared to the reference method across all read and inoculation methods.*

When evaluating performance of *Citrobacter* spp., one major error was observed with all read methods using the Turbidity inoculation method, resulting in a MAJ 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:

> *One Citrobacter spp. strain resulted in a major error with ceftazidime when compared to the reference method with all read methods and turbidity inoculation method.*

When evaluating performance *Klebsiella* spp., one very major error was observed with all read and inoculation methods, resulting in a VMJ rate of 1.6% (1/64), except the autoSCAN-4 read method using the Turbidity inoculation method which has two very major errors, resulting in a VMJ rate of 3.1% (2/64), which is not acceptable. This is addressed in the following limitation in the device labeling:

> *Due to the occurrence of very major errors with Klebsiella spp. and ceftazidime with the autoSCAN-4 read with turbidity inoculation, MIC results of 2 or 4 µg/mL should be confirmed by manual read prior to reporting.*

When evaluating performance of *Serratia* spp., a range of MAJ rates was observed with all read methods when using the Turbidity inoculation method: 0% (0/73) to 1.4% (1/73), which is acceptable. A range of MAJ rates was observed with all read methods when using the Prompt inoculation method: 4.1% (3/73) to 17.8% (13/73), which is not acceptable. This is addressed in a limitation in the device labeling (described above) to only test *Serratia* spp. with the turbidity inoculation method.

The overall EA and CA performance for *Pseudomonas aeruginosa* 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: 2.0% (3/151) to 4.6% (7/151). In addition, a range of VMJ rates were observed for the different read and inoculation methods: 0% (0/33) to 6.1% (2/33). Due to the lack of an intermediate interpretive criteria for ceftazidime with *P. aeruginosa,* further analysis of the errors is performed and adjustments are made by considering the MIC values where the errors occurred. All major errors generated with each inoculation and read method had an MIC value that was one doubling dilution from the reference result and thus in essential agreement (EA), except for four MIC values obtained with the WalkAway read method using the Prompt inoculation method resulting in an adjusted MAJ rate of 2.6% (4/151) which is acceptable. In addition, all very major errors generated with each inoculation and read method had an MIC value that was one doubling dilution from the reference result and thus in essential agreement (EA), except for one MIC value obtained with the autoSCAN-4 read method using the turbidity inoculation method resulting in an adjusted VMJ rate of 3.0% (1/33) which is not acceptable. This has been addressed in the following footnote to the performance characteristics table in the device labeling:

> *The major error rate for ceftazidime was high for P. aeruginosa with Prompt/WalkAway/Manual and turbidity/WalkAway/Manual read and inoculation methods. The very major error rate was high with turbidity/all reads and Prompt/autoSCAN-4. All major errors and very major errors were one dilution apart from the reference method and as such fall within essential agreement, with the exception of turbidity/autoSCAN-4/manual methods. Based on the essential agreement and lack of an intermediate breakpoint for ceftazidime, the adjusted major error rate for P. aeruginosa with Prompt/WalkAway/Manual and turbidity/Manual meets acceptance criteria, and the adjusted very major error rate for P. aeruginosa with Prompt/autoSCAN-4 and turbidity/WalkAway meets acceptance criteria. One P. aeruginosa strain was outside of essential agreement and resulted in a very major error compared to the reference method when using the turbidity/autoSCAN-4/manual methods.*

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 Ceftazidime

Inoculation/ Read Method	Organism Group	Total Evaluable for Trending	≥ 1 Dilution Lower # (%)	Exact # (%)	≥ 1 Dilution Higher # (%)	Percent Difference (95% CI)	Trending Noted
Prompt/ WalkAway	*Acinetobacter* spp.	48	13 (27.1)	24 (50.0)	11 (22.9)	-4.2% (-12.1 to 13.04)	No
	Enterobacterales	254	68 (26.8)	65 (25.6)	121 (47.6)	20.9% (12.5 to 28.8)	No
	P. aeruginosa	177	26 (14.7)	102 (57.6)	49 (27.7)	13.0% (4.5 to 21.3)	No
Prompt/ autoSCAN-4	*Acinetobacter* spp.	48	17 (35.4)	23 (47.9)	8 (16.7)	-18.8% (-35.0 to -1.1)	No
	Enterobacterales	218	74 (33.9)	63 (28.9)	81 (37.2)	3.2% (-5.7 to 12.1)	No
	P. aeruginosa	177	39 (22.0)	109 (61.6)	29 (16.4)	-5.7% (-13.8 to 2.6)	No
Prompt/ Manual	*Acinetobacter* spp.	48	11 (22.9)	28 (58.3)	9 (18.8)	-4.2% (-20.3 to 12.2)	No
	Enterobacterales	242	69 (28.5)	64 (26.5)	109 (45.0)	16.5% (8.0 to 24.8)	No
	P. aeruginosa	178	34 (19.1)	113 (63.5)	31 (17.4)	-1.7% (-9.7 to 6.4)	No
Turbidity/ WalkAway	*Acinetobacter* spp.	49	16 (32.7)	24 (49.0)	9 (18.4)	-14.3% (-30.6 to 3.0)	No
	Enterobacterales	213	79	73	61	-8.5%	No

Inoculation/ Read Method	Organism Group	Total Evaluable for Trending	≥ 1 Dilution Lower # (%)	Exact # (%)	≥ 1 Dilution Higher # (%)	Percent Difference (95% CI)	Trending Noted
			(37.1)	(34.3)	(28.6)	(-17.2 to 0.5)	
	P. aeruginosa	179	38 (21.2)	102 (57.0)	39 (21.8)	0.6% (-8.0 to 9.1)	No
Turbidity/ autoSCAN-4	*Acinetobacter* spp.	48	22 (45.8)	19 (39.6)	7 (14.6)	-31.3% (-47.0 to -13.0)	**Yes**
	Enterobacterales	206	85 (41.3)	73 (35.4)	48 (23.3)	-18.0% (-26.6 to -9.0)	No
	P. aeruginosa	177	52 (29.4)	105 (59.3)	20 (11.3)	-18.1% (-26.2 to -9.8)	No
Turbidity/ Manual	*Acinetobacter* spp.	47	16 (34.0)	25 (53.2)	6 (12.8)	-21.3% (-37.1 to -4.1)	No
	Enterobacterales	207	75 (36.2)	79 (38.2)	53 (25.6)	-10.6% (-19.3 to -1.7)	No
	P. aeruginosa	177	47 (26.6)	108 (61.0)	22 (12.4)	-14.1% (-22.2 to -5.9)	No

No trending was observed for *Acinetobacter* spp., *P. aeruginosa* or *Enterobacterales* organism groups with all inoculation and read methods, except for trending toward lower MIC values with *Acinetobacter* spp. using the turbidity inoculation / autoSCAN-4 read method. At a species level, a bias for higher MIC values was observed for *Proteus* spp. across all read methods and both inoculation methods, as well as *Serratia* spp. across all read methods with Prompt inoculation. A bias for lower MIC values was observed for *Citrobacter freundii* complex with all reads with the turbidity inoculation and *Klebsiella* spp. with the WalkAway and autoSCAN-4 reads with turbidity inoculation. These are addressed in the following footnotes to the performance table in the device labeling:

Ceftazidime MIC values for Enterobacterales were most frequently in exact agreement with the reference method. When not in agreement results tended to be one doubling dilution higher for Proteus spp. with all read/all inoculation methods and Serratia spp. with all read methods/Prompt inoculation. When not in agreement results tended to be one doubling dilution lower for Citrobacter freundii complex with all read methods/turbidity inoculation, and Klebsiella spp. with the WalkAway/autoScan-4/turbidity inoculation.

Ceftazidime MIC values for Acinetobacter spp. were most frequently in exact agreement with the reference method. When not in agreement results tended to be one doubling dilution lower for Acinetobacter spp. with the autoSCAN- 4/turbidity inoculation.

Resistance Mechanism Characterization

Challenge isolates of *Acinetobacter, Enterobacterales* and *P. aeruginosa* harboring various molecular mechanisms of resistance were tested with ceftazidime. 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:

The FDA-identified and recognized susceptibility interpretive criteria for ceftazidime are listed in **Table 6**.

Table 6: FDA-Identified and Recognized Interpretive Criteria for Ceftazidime (µg/mL)[a]

Organisms	S	I	R
Acinetobacter spp.	≤8	16	≥32
Enterobacteriaceae	≤4	8	≥16
Pseudomonas aeruginosa	≤8	-	≥16

[a]According to FDA STIC Website.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that Beckman Coulter intends to use to evaluate the MicroScan Dried Gram-Negative MIC/Combo Panels with Ceftazidime (Caz) (0.5 – 64 µg/mL) when revised breakpoints for ceftazidime are published on

the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Beckman Coulter will update the ceftazidime 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.