510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K172255

B. Purpose for Submission:

To obtain a substantial equivalence for the addition of ceftolozane/tazobactam at concentrations 0.25/4-16/4 µg/mL to the MicroScan Dried Gram negative MIC/Combo Panel for susceptibility testing of non-fastidious Gram negative organisms.

C. Measurand:

Ceftolozane/tazobactam 0.25/4-16/4 µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST) growth based detection

E. Applicant:

Beckman Coulter

F. Proprietary and Established Names:

MicroScan Dried Gram-Negative MIC/Combo Panels with Ceftolozane/tazobactam (0.25/4-16/4 µg/ml)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product codes:

   LTT – Panels, Test, Susceptibility, Antimicrobial

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

JWY – Manual Antimicrobial Susceptibility Test Systems

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended use(s):

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

2. Indication(s) for use:

   The MicroScan Dried Gram-Negative MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing 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 ceftolozane/tazobactam at concentrations of 0.25/4 to 16/4 µg/mL to the test panel.

   Ceftolozane/tazobactam has been shown to be active both clinically and *in vitro* against the following organisms:

   > *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis,* and *Pseudomonas aeruginosa*

   *In vitr*o data is available for the following organisms, but their clinical significance is unknown:

   > *Citrobacter koseri, Morganella morganii*, *Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Serratia liquefaciens,* and *Serratia marcescens*

3. Special conditions for use statement(s):

   For prescription use only

   The following information is included in labeling

   - *Results obtained with E. cloacae and ceftolozane/tazobactam have shown discrepant MICs when compared with the reference method when read by the MicroScan instruments. Therefore, prior to reporting, these isolate results should be interpreted manually.*

   - *Results obtained P. rettgeri and S. liquefaciens and ceftolozane/tazobactam have shown discrepant MICs when compared with the reference method when read by the WalkAway instrument and inoculated using the Prompt. Therefore, prior to reporting, these isolate results should be interpreted manually.*

   - *Ceftolozane/tazobactam results obtained with M. morganii and P. rettgeri isolates using the Prompt Inoculation system have shown potential major errors. Therefore, prior to reporting, isolates with resistant results should be retested using the turbidity inoculation method.*

   - *Ceftolozane/Tazobactam is not active against Enterobacteriaceae bacteria that produce metallo-beta lactamases and serine carbapenemases.*

4. Special instrument requirements:

   MicroScan panels can be read either manually or automatically on the WalkAway or autoScan-4 instrument systems. Inoculum suspensions can be determined manually or using the Prompt.

I. Device Description:

The MicroScan Dried Gram Negative MIC/Combo Panel with ceftolozane/tazobactam is used to determine the quantative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and faculative Gram-negative bacilli. After inoculation, panels are incubated for 16-20 hours at 35°C +/- 1°C in a non-CO_2 incubator, and read either visually or with MicroScan instrumentation, according to the package insert.

Primary incoulation method: Prompt; Alternate inoculation method: Turbidity

Primary read method: MicroScan WalkAway system; Alternate read methods: MicroScan autoSCAN-4 (AS4) instrument and manual reads

J. Substantial Equivalence Information:

1. Predicate device name(s):

   MicroScan Dried Gram-Negative MIC/Combo Panels with Imipenem (0.25 -8 µg/mL)

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

   K162740

3. Comparison with predicate:

Table 1. Comparison with Predicate Device

Similarities		
Item	Device: MicroScan Dried Gram-Negative MIC/Combo Panels – Ceftolozane/tazobactam (K172255)	Predicate: MicroScan Dried Gram-Negative MIC/Combo Panels - Imipenem (K162740)
Technology	Overnight microdilution MIC susceptibility	Same
Read Method	Manual and automated	Same
Inoculation Methods	Turbidity and Prompt	Same
Result Reported	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (S,I,R)	Same
Instrumentation	WalkAway or autoSCAN-4 Instrument systems	Same
Incubation	16-20 hours	Same

Differences		
Item	Device: MicroScan Dried Gram-Negative MIC/Combo Panels – Ceftolozane/tazobactam (K172255)	Predicate: MicroScan Dried Gram-Negative MIC/Combo Panels - Imipenem (K162740)
Antimicrobial agent	Ceftolozane/tazobactam	Imipenem
Concentration Range	0.25/4-16/4 µg/mL	0.25 – 8 µg/mL

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

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

2. CLSI M100-S027: Performance Standards for Antimicrobial Susceptibility Testing;

Twenty-Seventh Informational Supplement

3. CLSI M7-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition

L. Test Principle:

The MicroScan Dried Gram-Negative MIC/Combo Panels with Ceftolozane/tazobactam are antimicrobial susceptibility tests that are miniaturizations of the broth dilution susceptibility test which have been dehydrated. Various antimicrobial agents are diluted in Mueller Hinton broth supplemented wtih calcium and magnesium to concentrations bridging the range of clinical interest. Breakpoint Combo panels use concentrations equivalent to the categorical breakpoints of FDA and/or CLSI. After inoculation and rehydration with a standardized suspension of organism and incubation of 35°C +/- 1°C for a minimum of 16 hours, the minimum inhibitory concentration (MIC) for the test organism is determined by observing the lowest antimicrobial concentration showing inhibition of growth.

M. Performance Characteristics:

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was performed at three sites using 17 isolates of non-fastidious Gram negative organisms. The isolates were tested in triplicate over three different days using both inoculation methods (Prompt, turbidity) for each reading method (WalkAway, autoSCAN-4, manual). The isolates tested in the reproducibility study included *C. koseri* (1), *E. cloacae* (1), *E. coli* (5), *K. oxytoca* (2), *K. pneumoniae* (3), *P. aeruginosa* (3), *P. mirabilis* (1) and *S. marcescens* (1). The mode MIC value was pre-determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. There were no "off-scale" MIC results for any reading method versus inoculation method; therefore, only best case scenario is reported in Table 2 below. Reproducibility was calculated and was reported as greater than 95% for all combinations of reading methods and inoculation methods. The results (Table 2) were acceptable.

Table 2. Reproducibility Results with all inoculation and read methods.

Read Method	Prompt Inoculation	Turbidity Inoculation
WalkAway	453/459 (98.7%)	455/459 (99.1%)
autoSCAN-4	447/459 (97.4%)	451/459 (98.3%)
Manual	449/459 (97.8%)	447/459 (97.4%)

b. Linearity/assay reportable range:

Not Applicable

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

Quality Control Testing:
The QC isolates recommended by both FDA and CLSI, *E.coli* ATCC 25922, *E. coli* ATCC 35218, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853 were tested a sufficient number of times (i.e., at least 20/site) at each of three testing sites. They were tested using both turbidity and Prompt inoculation methods for the manual read, WalkAway instrument and autoSCAN 4 instruments. The results are summarized in Table 3 below. Greater than 95% of the results obtained for each inoculation method with each read method were acceptable.

Table 3. Quality Control Results – Ceftolozane/tazobactam

Organism	Conc (µg/mL)	Ref	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	Walk Away	AS4	Manual	Walk Away	AS4
E. coli ATCC 25922 Expected Result: 0.12/4 – 0.5/4 µg/mL	0.06		-	-	-	-	-	-
	0.12	44	11	32	20	19	46	37
	0.25	119	147	124	137	142	116	125
	0.5	1	6	6	6	2	1	1
	1	-	-	-	-	1	1	1
E. coli ATCC 35218 Expected Result: 0.06/4 – 0.25/4 µg/mL	≤0.03	-	-	-	-	-	-	-
	0.06	42	1	2	1	-	-	1
	0.12	112	142	151	144	153	160	157
	0.25	10	16	6	14	11	4	6
	0.5	-	3	2	2	-	-	-
	1	-	2	1	1	-	-	-
	2	-	-	-	-	-	-	-
K. pneumoniae ATCC 700603 Expected Result: 0.5/4 – 2/4 µg/mL	0.25	-	-	-	-	-	-	-
	0.5	10	-	-	-	1	3	-
	1	144	136	155	153	145	160	155
	2	10	25	5	8	16	1	7
	4	-	3	1	3	2	-	2
	8	-	-	-	-	-	-	-
P. aeruginosa ATCC 27853 Expected Result: 0.25/4 – 1/4 µg/mL	0.12	-	-	-	-	-	-	-
	0.25	9	-	-	-	1	2	-
	0.5	151	158	161	164	162	162	163
	1	4	6	-	-	1	-	-
	2	-	-	-	-	-	-	-

Inoculum Density Check:

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

for each organism tested. Colony counts were performed using the QC strain *E. coli* ATCC 25922 for both Prompt and Turbidity inoculation methods during QC testing.

In addition, data was also collected during the Reproducibility phase using the Prompt inoculum preparation method. Colony counts were performed weekly on the quality control strain *E. coli* ATCC 25922. Colony counts were also done once at each site for each Reproducibility isolate. All colony counts were acceptable.

Growth Failure Rate

The growth rate for all combinatinos of inoculation and read methods was 100%.

Purity Check:

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

Prompt Inoculation Validation:

An additional study was conducted to demonstrate that additional time after inoculating the Prompt would not have an impact on susceptibility testing prior to panel inoculation. Prompt bottles were inoculated with *C. koseri* and *S. liquefaciens* and tested at 0 (baseline) and 4 hours after inoculation. Panels were read by the WalkAway, AutoScan-4 and manually and compared to the reference method. When compared to baseline and reference results, the 4 hour incubation did not appear to affect *C. koseri* susceptibility results when read by any method. In addition, the 4 hour incubation did not appear to affect *S. liquefaciens* susceptibility results when compared to the reference and baseline when read manually only.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Results obtained with the MicroScan Dried Gram Negative MIC/Combo Panel for ceftolozane/tazobactam were compared to results obtained with the CLSI frozen broth

microdilution reference panel. The range of dilutions evaluated with the MicroScan panels was 0.25/4 to 16/4 µg/mL.

Two inoculation methods were used: the Prompt Inoculation System and the turbidity method. For the Prompt Inoculation System, inocula were prepared using the instructions of the manufacturer. For the turbidity method, inocula were standardized using the MicroScan Turbidity Meter to approximate a 0.5 McFarland turbidity standard. Reference panels were inoculated using the turbidity method. Each isolate was tested using both inoculation methods and read by the WalkAway instrument, autoSCAN-4 instrument, and read manually; however, the primary read that was identified as being used by most users was the WalkAway instrument with the Prompt inoculation.

Clinical:

Clinical testing was conducted at three sites using 394 fresh, 162 recent, and 19 stock Gram negative organisms for a cumulative of 575 isolates. These consisted of 496 *Enterobacteriaceae* isolates to include *E. cloacae* (48 isolates), *E. coli* (77), *S. liquefaciens* (1), *S. marcescens* (32), *C. koseri* (49), *K. oxytoca* (47), *K. pneumoniae* (88), *M. morganii* (41), *P. mirabilis* (56), *P. stuartii* (21), *P. rettgeri* (19) and *P. vulgaris* (17) and 79 *P. aeruginosa* isolates. All isolates tested are listed in the Indications for Use. Of these, 23 isolates were resistant to cefotolozane/tazobactam by the reference method.

Challenge:

Additional stock challenge isolates were tested at an external study site. These isolates consisted of organisms with known resistance mechanisms (e.g., isolates obtained from FDA/CDC AR bank) to challenge the ability of AST system to correctly identify the susceptibility category. Challenge testing was conducted using 118 Gram negative organisms, consisting of 20 *P. aeruginosa* isolates,and 98 *Enterobacteriaceae* including *E. cloacae* (13 isolates), *E. coli* (20), *S. liquefaciens* (10), *S. marcescens* (4), *C. koseri* (13), *K. oxytoca* (8), *K. pneumoniae* (18), *M. morganii* (3), *P. mirabilis* (7), *P. stuartii* (1), and *P. vulgaris* (1). Of these 118 Gram negative organisms, 40 were resistant to ceftolozane/tazobactam by the reference method.

594 Enterobacteriaceae and 99 P. aeruginosa isolates (Clinical and Challenge) isolates were evaluated. Tables 3, 4, 5, and 6 below illustrate the performance of testing Ceftolozane/tazobactam on the WalkAway, autoSCAN-4, and manual reads using the Prompt and turbidity inoculation methods, respectively.

Table 3. Combined (Clinical and Challenge) Performance Summary of Gram Negative Panels with *Enterobacteriaceae* – Prompt Inoculation Method, All Read Methods

Panel Reading Method	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min (%)	maj (%)	vmj (%)
WalkAway	594	545	91.8	93	68	73.1	563	94.8	55	10 (1.7%)	19 (3.6%)	2 (3.6%)
autoSCAN-4	594	561	94.4	97	78	80.4	576	97	55	9 (1.5%)	7 (1.3%)	2 (3.6%)
Manual	594	565	95.1	105	92	87.6	577	97.1	55	10 (1.7%)	6 (1.1%)	1 (1.8%)

Table 4. Combined (Clinical and Challenge) Performance Summary of Gram Negative Panels with *P. aeruginosa* – Prompt Inoculation Method, All Read Methods

Panel Reading Method	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min (%)	maj (%)	vmj (%)
WalkAway	99	98	99	73	72	98.6	97	98	8	2 (2%)	0	0
autoSCAN-4	99	97	98	74	72	97.3	97	98	8	2 (2%)	0	0
Manual	99	95	96	74	70	94.6	95	96	8	4 (4%)	0	0

Table 5. Combined (Clinical and Challenge) Performance Summary of Gram Negative Panels with *Enterobacteriaceae* – Turbidity Inoculation Method, All Read Methods

Panel Reading Method	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min (%)	maj (%)	vmj (%)
WalkAway	594	569	95.8	96	76	79.2	581	97.8	55	10 (1.7%)	2 (0.4%)	1 (1.8%)
autoSCAN-4	594	568	95.6	102	83	81.4	583	98.1	55	7 (1.2%)	3 (0.6%)	1 (1.8%)
Manual	594	573	96.5	116	102	87.9	583	98.1	55	5 (0.8%)	6 (1.1%)	0

Table 6. Combined (Clinical and Challenge) Performance Summary of Gram Negative Panels with *P. aeruginosa* – Turbidity Inoculation Method, All Read Methods

Panel Reading Method	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min (%)	maj (%)	vmj (%)
WalkAway	99	99	100	70	70	100	97	98	8	2 (2%)	0	0
autoSCAN-4	99	94	94.9	73	68	93.2	97	98	8	2 (2%)	0	0
Manual	99	96	97	74	71	95.9	96	97	8	3 (3%)	0	0

EA - Essential Agreement
CA - Category Agreement
R - resistant isolates
maj – major discrepancies
vmj - very major discrepancies
min – minor discrepancies

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

As seen in Tables 3, 4, 5, and 6, the percent EA overall for combined clinical and challenge isolates was above 90% for all read methods and inoculation methods with the exception of some organisms within the *Enterobacteriaceae* family when inoculated with the Prompt. Specifically, *E. cloacae* demonstrated a performance of 83.6% (51/61) and 86.9% (53/61) when read by the WalkAway and AS-4 instruments but when read manually, the EA increased to 90.2% (55/61). Therefore, for this organism, the following limitation is included in the labeling:

Results obtained with E. cloacae and ceftolozane/tazobactam have shown discrepant MICs when compared with the reference method when read by the MicroScan instruments. Therefore, prior to reporting, these isolate results should be interpreted manually.

M. morganii, *P. rettgeri*, and *S. liquefaciens* isolates also demonstrated less than 90% EA [82.0% (50/61), 77.3% (34/44), 78.9% (15/19), and 36.4% (4/11) respectively] when read by the WalkAway and inoculated using the Prompt. When the same plates were reviewed manually, the EA when testing *P. rettgeri* and *S. liquefaciens* isolates surpassed 90% [100% (19/19) and 100% (11/11) respectively]. Therefore, for these two isolates, the following limitation is included in the labeling:

Results obtained P. rettgeri and S. liquefaciens and ceftolozane/tazobactam have shown discrepant MICs when compared with the reference method when read by the WalkAway instrument and inoculated using the Prompt. Therefore, prior to reporting, these isolate results should be interpreted manually.

In addition, isolates of *M. morganii* demonstrated high major error (MAJ) rates when inoculated with the Prompt and read by the WalkAway [15.9% (7/44)]. When these isolates were retested using the turbidity method, they were able to meet 90% EA with the WalkAway [95.5% (42/44)] and demonstrated no MAJ errors (0%). Therefore, the following limitation is included in the labeling:

Ceftolozane/tazobactam results obtained with M. morganii isolates using the Prompt Inoculation system have shown potential major errors. Therefore, prior to reporting, isolates with resistant results should be retested using the turbidity inoculation method.

The MAJ error rate for *Enterobacteriaceae* with the WalkAway and Prompt is 3.6%; however, when *M. morganii* isolates were retested using the turbidity method, the MAJ error rate decreased to 2.3% which is acceptable. In addition, the VMJ error rate decreased from 3.6% to 1.8% when *P. rettgeri* isolates were read manually and therefore, acceptable.

As seen in Tables 3, 4, 5, and 6, the percent CA overall for combined clinical and challenge isolates was above 90%, and is therefore acceptable as described in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 2009*. However, when interpreted by the WalkAway and inoculated with the Prompt, *M. morganii*, *P. rettgeri*, and *S. liquefaciens* isolates demonstrated lower than adequate CA performance when analyzed separately [i.e., 81.8% (36/44), 84.2% (16/19), and 45.5% (5/11) respectively] and yielded high major error rates as mentioned above. The CA rates significantly improved when *M. morganii* isolates were repeated with the turibidity inoculation (100%), and when *P. rettgeri* (100%) and *S. liquefaciens* (100%) isolates were interpreted manually.

MIC Trends:

Table 7. Summary of Evaluation of MIC Trends (combined clinical and challenge data)

Ceftolozane/ tazobactam	Total	≥1 dil lower	Exact	≥1 dil higher
WalkAway/Prompt				
Enterobacteriaceae[a]	**576**	**100 (17.36%)**	**299 (51.96%)**	**177 (30.73%)**
P. aeruginosa	**98**	**14 (14.29%)**	**75 (76.53%)**	**9 (9.18%)**

[a]Difference between the higher and lower dilutions is 13.37%; 95% C.I. (8.46% to 18.20%)

As illustrated in Table 7, there was a difference in in results trending above the reference for *Enterobacteriaceae* using the WalkAway read method and Prompt inoculation method. The data demonstrates a trend for one doubling dilution higher for these results compared to the reference method and therefore, the following is included as a footnote in the labeling:

Ceftolozane/tazobactam MIC values for Enterobacteriaceae isolates tended to be one doubling dilution higher when read by the WalkAway and using the Prompt inoculation method.

b. Matrix comparison:

N/A

3. Clinical studies:

a. Clinical Sensitivity:

N/A

b. Clinical specificity:

N/A

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

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Ceftolozane/tazobactam are as listed in Table 8.

Table 8. Interpretive Criteria for Ceftolozane/tazobactam (µg/mL)

	Susceptible (S)	Intermediate (I)	Resistant (R)
Enterobacteriaceae	≤2/4	4/4	≥8/4
P. aeruginosa	≤4/4	8/4	≥16/4

N. Proposed Labeling:

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

O. Conclusion:

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