510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K250036

B Applicant

Beckman Coulter, Inc.

C Proprietary and Established Names

MicroScan Dried Gram-Positive MIC/Combo Panels with Daptomycin (DAP) (0.06-32 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 daptomycin at concentrations of 0.06-32 µg/mL with the MicroScan Dried Gram-Positive MIC/Combo Panels for susceptibility testing of non-fastidious gram-positive organisms.

B Measurand:

Daptomycin in the dilution range of 0.06-32 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 Positive MIC/Combo, Dried Gram Positive Breakpoint Combo panels. MicroScan Positive panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of rapidly growing aerobic and facultative gram-positive cocci, some fastidious aerobic gram-positive cocci and *Listeria monocytogenes*.

B Indication(s) for Use:
The MicroScan Dried Gram-Positive 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 gram-positive cocci, some fastidious aerobic gram-positive cocci and *Listeria monocytogenes*. 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 daptomycin at concentrations of 0.06-32 µg/mL to the test panel. Testing is indicated for *Enterococcus faecium, Enterococcus* spp. other than *E. faecium,* and *Staphylococcus* spp., as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC) webpage.

The MicroScan Dried Gram-Positive MIC/Combo Panels with Daptomycin (Dap) (0.06-32 µg/mL) has demonstrated acceptable performance with the following organisms:

Enterococcus faecium

Enterococcus spp. other than *E. faecium* (*Enterococcus faecalis, Enterococcus avium, Enterococcus raffinosus, Enterococcus casseliflavus* and *Enterococcus durans*)

Staphylococcus spp. (*Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus capitis, Staphylococcus haemolyticus, Staphylococcus lugdunensis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus simulans, Staphylococcus saprophyticus, Staphylococcus intermedius*, and *Staphylococcus sciuri*)

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

Performance of daptomycin when testing *Enterococcus faecium* using the Prompt inoculation method and WalkAway read method showed unacceptable adjusted potential major error rates compared to the reference method (6.3%, 4/63). Due to the occurrence of potential major errors

with *E. faecium* and daptomycin with the WalkAway read with prompt inoculation, MIC results of ≥8 µg/mL should be confirmed by manual read prior to reporting.

Performance of daptomycin when testing *Staphylococcus capitis* and *Staphylococcus hominis* using the turbidity inoculation method with autoSCAN-4 read method was outside of essential agreement compared to the reference method. *S. capitis* and *S. hominis* species when using the turbidity inoculation method should only be read with the WalkAway and manual read methods.

Performance of daptomycin when testing *Staphylococcus simulans* and *Staphylococcus warneri* using the Prompt inoculation method with all read methods was outside of essential agreement compared to the reference method. *S. simulans* and *S. warneri* species should only be tested with the turbidity inoculation method.

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-Positive MIC/Combo Panel with daptomycin is used to determine the quantitative and/or qualitative antimicrobial agent susceptibility of rapidly growing aerobic and facultative gram-positive cocci colonies grown on solid media. After inoculation, panels are incubated for 16-20 hours at 35°C ± 1°C in a non-CO2 incubator and read either visually or with MicroScan instrumentation according to the package insert.

Inoculation methods: Turbidity 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 Positive MIC/Combo Panels with Vancomycin (0.25-64 µg/mL)

B Predicate 510(k) Number(s):

K150039

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K250036	Predicate: K150039
Device Trade Name	MicroScan Dried Gram-Positive MIC/Combo Panels with Daptomycin (Dap) (0.06-32 µg/mL)	MicroScan Dried Gram-Positive MIC/Combo Panels with Vancomycin (0.25-64 µg/mL)
General Device Characteristic Similarities		
Intended Use/Indications For Use	Determination of susceptibility with Gram-positive bacteria	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 with appropriate categorical interpretation	Same
General Device Characteristic Differences		
Antimicrobial Agent	Dried Daptomycin 0.06-32 µg/mL	Dried Vancomycin 0.25-64 µg/mL
Tested species	*Enterococcus faecium* *Enterococcus* spp. other than *E. faecium (Enterococcus faecalis, Enterococcus avium, Enterococcus raffinosus, Enterococcus casseliflavus* and *Enterococcus durans)* *Staphylococcus* spp. *(Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus capitis, Staphylococcus haemolyticus, Staphylococcus lugdunensis, Staphylococcus hominis, Staphylococcus warneri, Staphylococcus simulans, Staphylococcus saprophyticus,*	*Enterococci* (e.g., *Enterococcus faecalis*) *Staphylococci*, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogenous methicillin-resistant strains)

Device & Predicate Device(s):	Device: K250036	Predicate: K150039
	Staphylococcus intermedius, and *Staphylococcus sciuri)*	

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 four clinical sites using 12 isolates of gram-positive isolates that were consistent with the device intended use. The range of daptomycin dilutions tested was 0.06-32 µg/mL. Isolates were tested in triplicate over three days at four clinical sites (36 data points per isolate) for a total of 431 data points (due to one replicate failure). The isolates tested in the reproducibility study included four (4) isolates of *Staphylococcus aureus* and eight (8) isolates of *Enterococcus faecalis.*

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 Daptomycin 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	428/431 (99.3)	428/431 (99.3)	430/431 (99.8)	430/431 (99.8)
autoSCAN-4	422/431 (97.9)	422/431 (97.9)	421/431 (97.7)	421/431 (97.7)
Manual	429/431 (99.5)	429/431 (99.5)	430/431 (99.8)	430/431 (99.8)

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 *S. aureus* ATCC 29213 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 *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212, 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 *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 were tested with all inoculation and read methods using ten (10) dilutions of daptomycin (0.06-32 µg/mL). The reference panel was inoculated using the turbidity method only. In this submission, the QC ranges for both *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 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 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 Daptomycin

Organism	Conc. (µg/mL)	Reference [1]	Prompt Inoculation Method			Turbidity Inoculation Method		
			autoSCAN-4	Manual	WalkAway	autoSCAN-4	Manual	WalkAway
S. aureus ATCC 29213 Expected Range 0.12-1 µg/mL	≤ 0.06							
	0.12	14	1	1	1	4	3	4
	0.25	210	70	65	67	217	216	219
	0.5	5	146	150	152	4	6	3
	1		9	13	9	4	4	4
	2							
	4		1	1	1			
	8							
	16							
	32							
	> 32							
E. faecalis ATCC 29212 Expected Range 1-4 µg/mL	≤ 0.06					1		
	0.12							
	0.25							
	0.5							
	1	46	14	11	1	11	6	1
	2	181	124	112	107	178	170	177
	4	1	92	106	121	39	52	50
	8				1			1
	16							
	32							
	> 32							

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

6. Detection Limit:

   Not applicable

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

   The results obtained with the MicroScan Dried Gram-Positive MIC/Combo Panel with Daptomycin (0.06-32 µg/mL) were compared to results obtained using a frozen broth microdilution reference panel (dilution range 0.06-32 µg/mL). Clinical isolates were evaluated at four testing sites in the U.S.; challenge isolates were evaluated at one internal and one external site.

   The reference panel was prepared as described in CLSI document M07-A11 except for the use of Pluronic-F (wetting agent) in the inoculum water for the reference panel. A summary of historical data from previously cleared antimicrobial tests was provided in the submission which demonstrated that inclusion of the wetting agent did not affect testing. In addition, QC testing conducted during the clinical study was acceptable.

For the reference method and MicroScan panels inoculated using the turbidity method, panels were inoculated using the same standardized suspension further diluted into 25 mL of inoculum water with Pluronic-D (for the MicroScan panels) or Pluronic-F (for the frozen reference panels). MicroScan panels were also inoculated using the Prompt inoculation method with isolates inoculated into the Prompt inoculation bottle. Reference panels were read manually (visually) after 16-20 hours. MicroScan panels inoculated with both inoculation methods were read using the WalkAway and autoSCAN-4 instruments and by manual read after 16-20 hours.

Clinical Study
To determine the performance of MicroScan Dried Gram-Positive MIC/Combo Panels with Daptomycin, a total of 950 gram-positive clinical isolates were evaluated with the Prompt inoculation method and the Turbidity inoculation method and all read methods at four clinical sites. Isolates included *Enterococcus faecium* (51 isolates), *Enterococcus* spp. other than *E. faecium* [118 isolates including *E. avium* (3), *E. casseliflavus* (2), *E. durans* (2), *E. faecalis* (92), *E. gallinarum* (3), *E. raffinosus* (3), and *Enterococcus* spp. (13)]
, and *Staphylococcus* spp. [781 isolates including *S. aureus* (414), *S. auricularis* (2) *S. capitis* (13), *S. epidermidis* (205), *S. equorum* (1), *S. haemolyticus* (39), *S. hominis* (20), *S. intermedius* (2), *S. lugdunensis* (28), *S. saprophyticus* (9), *S. sciuri* (1), *S. simulans* (10), *S. warneri* (14), and *Staphylococcus* spp. (23)].

Of the 950 clinical isolates with results included in the performance analysis, 690 (72.6%) were recent/contemporary isolates (isolated from clinical specimens and tested within six months of isolation with minimal sub-culturing), and 260 (27.4%) were stock isolates.

Challenge Study
A total of 121 gram-positive challenge isolates from species with STIC-recognized breakpoints were evaluated at two sites including *Enterococcus faecium* (36 isolates), *Enterococcus faecalis* (35 isolates), and *Staphylococcus aureus* (50 isolates).

Results for essential agreement, category agreement, and categorical errors for *E. faecium*, *Enterococcus* spp. other than *E. faecium,* and *Staphylococcus* spp. for all inoculation and read methods are shown in **Table 3** and **Table 4** below. Essential agreement of evaluable results was calculated considering MIC results that were clearly identical to reference method results or clearly one doubling dilution higher or lower than the reference method results. Performance was evaluated separately for each organism group (i.e., *E. faecium*, *Enterococcus* spp. other than *E. faecium*, and *Staphylococcus* spp.) in accordance with the appropriate susceptibility test interpretive criteria for each group. Data for all species within a group were analyzed for performance separately and combined in accordance with the STIC-recognized breakpoints for the group then presented combined as shown in **Table 3** and **Table 4**. Footnotes and limitations were applied in labeling as appropriate.

Table 3. Performance of MicroScan Dried Gram-Postive Panels with Daptomycin, 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													
***Staphylococcus* spp., ≤1 (S)**													
Clinical	781	726	93.0	757	702	92.7	779	99.7	2	779	0	0	1
Challenge	50	50	100	50	50	100	48	96.0	19	31	0	0	0
Combined	831	776	93.4	807	752	93.2	827	99.5	21	810	0	0	1
***Enterococcus faecium*, ≤4 (SDD), ≥8 (R)**													
Clinical	51	47	92.2	49	45	91.8	46	90.2	2	49	0	2	0
Challenge	36	36	100	36	36	100	36	100	22	14	0	0	0
Combined	87	83	95.4	85	81	95.3	82	94.3	24	63	0	2	0
***Enterococcus* spp. other than *E. faecium*, ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	118	115	97.5	117	114	97.4	114	96.6	0	116	4	0	0
Challenge	35	34	97.1	34	33	97.1	31	88.6	8	23	3	0	1
Combined	153	149	97.4	151	147	97.4	145	94.8	8	139	7	0	1
Manual Read													
***Staphylococcus* spp., ≤1 (S)**													
Clinical	781	725	92.8	765	709	92.7	780	99.9	2	779	0	0	0
Challenge	50	49	98.0	50	49	98.0	48	96.0	19	31	0	0	0
Combined	831	774	93.1	815	758	93.0	828	99.6	21	810	0	0	0
***Enterococcus faecium*, ≤4 (SDD), ≥8 (R)**													
Clinical	51	48	94.1	49	46	93.9	47	92.2	2	49	0	2	0
Challenge	36	36	100	36	36	100	36	100	22	14	0	0	0
Combined	87	84	96.6	85	82	96.5	83	95.4	24	63	0	2	0
***Enterococcus* spp. other than *E. faecium*, ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	118	117	99.2	117	116	99.2	113	95.8	0	116	5	0	0
Challenge	35	35	100	34	34	100	31	88.6	8	23	4	0	0
Combined	153	152	99.4	151	150	99.3	144	94.1	8	139	9	0	0
WalkAway Read													
***Staphylococcus* spp., ≤1 (S)**													
Clinical	781	734	94.0	763	716	93.8	779	99.7	2	779	0	0	0
Challenge	50	50	100	50	50	100	48	96.0	19	31	0	0	0
Combined	831	784	94.3	813	766	94.2	827	99.5	21	810	0	0	0
***Enterococcus faecium*, ≤4 (SDD), ≥8 (R)**													
Clinical	51	43	84.3	49	41	83.7	44	86.3	2	49	0	4	0
Challenge	36	36	100	36	36	100	36	100	22	14	0	0	0
Combined	87	79	90.8	85	77	90.6	80	92.0	24	63	0	4	0
***Enterococcus* spp. other than *E. faecium*, ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	118	118	100	117	117	100	113	95.8	0	116	5	0	0
Challenge	35	35	100	34	34	100	31	88.6	8	23	4	0	0
Combined	153	153	100	151	151	100	144	94.1	8	139	9	0	0

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-Positive 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-Positive MIC/Combo Panel.

Table 4. Performance of MicroScan Dried Gram-Positive Panels with Daptomycin, 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													
***Staphylococcus* spp., ≤1 (S)**													
Clinical	781	760	97.3	734	713	97.1	778	99.6	2	779	0	1	2
Challenge	50	50	100	50	50	100	49	98.0	19	31	0	0	0
Combined	831	810	97.5	784	763	97.3	827	99.5	21	810	0	1	2
***Enterococcus faecium*, ≤4 (SDD), ≥8 (R)**													
Clinical	51	48	94.1	49	46	93.9	50	98.0	2	49	0	0	0
Challenge	36	36	100	36	36	100	35	97.2	22	14	0	0	0
Combined	87	84	96.6	85	82	96.5	85	97.7	24	63	0	0	0
***Enterococcus* spp. other than *E. faecium*, ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	118	113	95.8	117	112	95.7	115	97.5	0	116	3	0	0
Challenge	35	35	100	34	34	100	35	100	8	23	0	0	0
Combined	153	148	96.7	151	146	96.7	150	98.0	8	139	3	0	0
Manual Read													
***Staphylococcus* spp., ≤1 (S)**													
Clinical	781	775	99.2	748	742	99.2	780	99.9	2	779	0	0	0
Challenge	50	50	100	50	50	100	49	98.0	19	31	0	0	0
Combined	831	825	99.3	798	792	99.3	829	99.8	21	810	0	0	0
***Enterococcus faecium*, ≤4 (SDD), ≥8 (R)**													
Clinical	51	51	100	49	49	100	50	98.0	2	49	0	0	0
Challenge	36	36	100	36	36	100	35	97.2	22	14	0	0	0
Combined	87	87	100	85	85	100	85	97.7	24	63	0	0	0
***Enterococcus* spp. other than *E. faecium*, ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	118	117	99.2	117	116	99.2	115	97.5	0	116	3	0	0
Challenge	35	35	100	34	34	100	33	94.3	8	23	2	0	0
Combined	153	152	99.4	151	150	99.3	148	96.7	8	139	5	0	0
WalkAway Read													
***Staphylococcus* spp., ≤1 (S)**													
Clinical	781	772	98.9	743	734	98.8	779	99.7	2	779	0	0	1
Challenge	50	50	100	50	50	100	49	98.0	19	31	0	0	0
Combined	831	822	98.9	793	784	98.9	828	99.6	21	810	0	0	1
***Enterococcus faecium*, ≤4 (SDD), ≥8 (R)**													
Clinical	51	48	94.1	49	46	93.9	49	96.1	2	49	0	1	0
Challenge	36	36	100	36	36	100	34	94.4	22	14	0	0	0
Combined	87	84	96.6	85	82	96.5	83	95.4	24	63	0	1	0
***Enterococcus* spp. other than *E. faecium*, ≤2 (S), 4 (I), ≥8 (R)**													
Clinical	118	117	99.2	117	116	99.2	116	98.3	0	116	2	0	0
Challenge	35	35	100	34	34	100	32	91.4	8	23	3	0	0
Combined	153	152	99.4	151	150	99.3	148	96.7	8	139	5	0	0

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-Positive 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-Positive MIC/Combo Panel.

Enterococcus faecium

The overall EA and CA performance for *Enterococcus faecium* 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 methods with the Prompt inoculation method: 4.8% (3/63) to 9.5% (6/63), which is not acceptable. In addition, a range of VMJ rates were observed for the different read and inoculation methods: 4.2% (1/24) to 12.5% (3/24), which is not acceptable. Since there is no defined susceptible interpretive category (S) for daptomycin with *Enterococcus faecium*, the susceptible-dose dependent (SDD) category is treated as an S for performance analysis. Due to the lack of intermediate interpretive criteria, further analysis of the errors was performed and adjustments were made by considering the MIC values of the errors compared to the reference MIC value. All very major errors had an MIC value that was in essential agreement with the reference MIC value. Therefore, the adjusted VMJ rate is 0.0% (0/24), which is acceptable.

Some major errors had an MIC value that was in essential agreement with the reference method. After adjustment, there remained two (2) major errors for the autoSCAN-4 and Manual read methods when using the prompt inoculation method resulting in an adjusted MAJ rate of 3.2% (2/63), which is acceptable. However, four (4) major errors remained with the WalkAWay read method when using the prompt inoculation method, resulting in an adjusted MAJ rate of 6.3% (4/63), which is not acceptable. This is addressed with the following limitation in the device labeling:

> *Performance of daptomycin when testing Enterococcus faecium using the Prompt inoculation method and WalkAway read method showed unacceptable adjusted potential major error rates compared to the reference method (6.3%, 4/63). Due to the occurrence of potential major errors with E. faecium and daptomycin with the WalkAway read with Prompt inoculation, MIC results of ≥8 µg/mL should be confirmed by manual read prior to reporting.*

The following footnotes were also added to the performance characteristics table:

> *The overall potential major error rate for daptomycin and E. faecium with the autoSCAN-4 and Prompt inoculation was 6.3% (4/63) and 4.8% (3/63) for manual reads with Prompt inoculation. Some potential major errors were one dilution apart from the reference method are within essential agreement. Based on the essential agreement and lack of an intermediate breakpoint for daptomycin, the adjusted potential major error rate for E. faecium is 3.2% (2/63) for the autoSCAN-4 and manual reads with Prompt inoculation. The adjusted potential major error rate is considered acceptable for the autoSCAN-4 and manual reads with Prompt inoculation.*
>
> *The overall potential very major error rate for daptomycin and E. faecium with Prompt and turbidity inoculation across all read methods (WalkAway, autoSCAN-4, and manual) ranged from 4.2% (1/24) to 12.5% (3/24). All potential very major errors were one dilution apart from the reference method and are within essential agreement. Based on the essential agreement and the lack of an intermediate breakpoint for daptomycin, the adjusted potential very major error rate for E. faecium is 0% (0/24).*

Enterococcus* spp. other than *E. faecium

The overall EA and CA performance for *Enterococcus* spp. other than *E. faecium* for the WalkAway, autoSCAN-4, and manual read methods were acceptable (>90%) for each inoculation method. No major errors were observed. One very major error was observed for an *E. faecalis* isolate with autoSCAN-4 read method using the Prompt inoculation method, resulting in a VMJ rate of 12.5% (1/8), which is not acceptable. Due to the limited number of resistant isolates tested, the error was considered random. This is addressed with the following footnote to the performance characteristics table in the device labeling:

> *One very major error (VMJ) was observed with daptomycin when testing Enterococcus faecalis with the Prompt inoculation and autoSCAN-4 read method that resulted in an unacceptable VMJ rate (12.5%, 1/8). This was considered random due to the limited number of resistant E. faecalis isolates tested.*

***Staphylococcus* spp.**

The overall EA and CA performance for *Staphylococcus* spp. for the WalkAway, autoSCAN-4, and manual read methods were acceptable (>90%) for each inoculation method. A range of potential MAJ rates were observed for the different read and inoculation methods: 0.1% (1/808) to 0.2% (2/808), which is acceptable. One (1) potential very major error was observed for the Prompt and turbidity inoculation methods with all read methods, resulting in a potential VMJ rate of 5% (1/20), which is not acceptable. These are considered potential errors because no interpretive category other than "susceptible only" is defined for *Staphylococcus* spp. with daptomycin. Due to the lack of an intermediate interpretive criteria, further analysis of the errors is performed and adjustments are made by considering the MIC values where the errors occurred. All potential major errors had an MIC value that was in essential agreement with the reference MIC value, except for one MIC value obtained with the autoScan-4 read method using the turbidity inoculation method. This resulted in a adjusted potential MAJ rate of 0.1% (1/808), which is acceptable. In addition, all potential very major errors had an MIC value that was in essential agreement with the reference MIC value, except for one MIC value obtained with the autoSCAN-4 read method using the Prompt and turbidity inoculation methods. This resulted in an adjusted potential VMJ rate of 5.0% (1/20) which is not acceptable. When evaluating by individual species, the one (1) adjusted potential very major error was due to *S. capitis*. Due to the limited number of resistant isolates tested with this species (one resistant isolate), the error was considered random. This is addressed in the following footnote to the performance characteristics table in the device labeling:

> *Two adjusted potential very major errors (VMJ) were observed with daptomycin when testing S. capitis and S. auricularis with the turbidity and Prompt inoculation with the autoSCAN-4 read method that resulted in an unacceptable adjusted potential VMJ rate (100%, 1/1 per species). These were considered random due to the limited number of resistant S. capitis and S. auricularis isolates tested.*

Device performance was also evaluated by individual species with STIC-recognized breakpoints within the *Staphylococcus* spp. reporting group. All species that demonstrated acceptable performance, with acceptable mitigations as described below, were included in the indications for use.

When evaluating performance of *S. capitis*, the autoSCAN-4 read and turbidity inoculation method demonstrated an EA of 84.6%, which is not acceptable, and a CA of 92.3%. When evaluating performance of *S. hominis*, the autoSCAN-4 read and Turbidity inoculation method demonstrated an EA rate of 85.0%, which is not acceptable, and a CA of 100%. This is addressed with the following limitation in the device labeling:

> *Performance of daptomycin when testing Staphylococcus capitis and Staphylococcus hominis using the turbidity inoculation method with autoSCAN-4 read method was outside of essential agreement compared to the reference method. S. capitis and S. hominis species when using the turbidity inoculation method should only be read with the WalkAway and manual read methods.*

When evaluating performance of *S. simulans*, the Prompt inoculation method demonstrated unacceptable EA with all read methods (autoSCAN-4 EA 70%, WalkAway EA 80%, manual EA 80%) with acceptable CA (100% for all read methods). When evaluating performance of *S. warneri* the Prompt inoculation method demonstrated unacceptable EA with all read methods (autoSCAN-4 EA 78.6%, WalkAway EA 78.6%, manual EA 85.7%) with acceptable CA (100% for all read methods). This is addressed with the following limitation in the device labeling:

> *Performance of daptomycin when testing Staphylococcus simulans and Staphylococcus warneri using the Prompt inoculation method with all read methods was outside of essential agreement compared to the reference method. S. simulans and S. warneri species should only be tested the turbidity inoculation method.*

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 Daptomycin

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	*Staphylococcus* spp.	823	102, (12.4)	364 (44.2)	357, (43.4)	31%, (27 to 35)	Yes
	Enterococcus faecium	85	9, (10.6)	48 (56.5)	28, (32.9)	22%, (10 to 34)	No
	Other *Enterococcus* spp.	152	18, (11.8)	88 (57.9)	46, (30.3)	18%, (9 to 27)	No
Prompt/ Manual	*Staphylococcus* spp.	827	63, (7.6)	372 (45.0)	392, (47.4)	40%, (36 to 44)	Yes
	Enterococcus faecium	85	3, (3.5)	57 (67.1)	25, (29.4)	26%, (15 to 37)	No
	Other *Enterococcus* spp.	153	14, (9.2)	93 (60.7)	46, (30.1)	21%, (12 to 29)	No
Prompt/ WalkAway	*Staphylococcus* spp.	823	88, (10.7)	372 (45.2)	363, (44.1)	33%, (29 to 37)	Yes
	Enterococcus faecium	85	5, (5.9)	46 (54.1)	34, (40.0)	34%, (22 to 45)	Yes
	Other *Enterococcus* spp.	152	25, (16.5)	105 (69.0)	22, (14.5)	-2%, (-10 to 6)	No
Turbidity/ autoSCAN-4	*Staphylococcus* spp.	815	280, (34.4)	498 (61.1)	37, (4.5)	-29%, (-33 to -26)	No
	Enterococcus faecium	85	13, (15.3)	52 (61.2)	20, (23.5)	8%, (-4 to 20)	No
	Other *Enterococcus* spp.	152	25, (16.5)	105 (69.0)	22, (14.5)	-2%, (-10 to 6)	No
Turbidity/ Manual	*Staphylococcus* spp.	815	234, (28.7)	534 (65.5)	47, (5.8)	-23%, (-26 to -19)	No
	Enterococcus faecium	85	9, (10.6)	66 (77.6)	10, (11.8)	1%, (-9 to 11)	No
	Other *Enterococcus* spp.	152	19, (12.5)	111 (73.0)	22, (14.5)	2%, (-6 to 10)	No
Turbidity/ WalkAway	*Staphylococcus* spp.	815	266, (32.6)	511 (62.7)	38, (4.7)	-28%, (-31 to -24)	No
	Enterococcus faecium	85	9, (10.6)	54 (63.5)	22, (25.9)	15%, (4 to 27)	No
	Other *Enterococcus* spp.	152	17, (11.2)	110 (72.3)	25, (16.5)	5%, (-3 to 13)	No

A bias for higher MIC values was observed for *Enterococcus faecium* with WalkAway and the Prompt inoculation method, and for *Staphylococcus aureus* with all read methods and the Prompt inoculation method. These are addressed in the following footnotes to the performance table in the device labeling:

Daptomycin MIC values for Staphylococcus spp. and E. faecium were most frequently in exact agreement with the reference method with prompt inoculation. When not in agreement results tended to be one or more doubling dilution higher for Staphylococcus spp. across all read methods and for E. faecium with the WalkAway.

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 Daptomycin (µg/mL)

Organisms	Interpretive Criteria[a]			
	S	SDD	I	R
Staphylococcus spp.	≤1	-	-	-
E. faecium	-	≤4	-	≥8
Enterococcus spp. other than *E. faecium*	≤2	-	4	≥8

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-Positive MIC/Combo Panels with Daptomycin (DAP) (0.6-32 µg/mL) device when revised breakpoints for daptomycin 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-Positive MIC/Combo Panels with Daptomycin (DAP) (0.6-32 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.