

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k043545

B. Purpose for Submission:

Addition of daptomycin to the MicroScan® Dried Gram-Positive MIC/Combo Panels

C. Measurand:

Daptomycin 0.03 - 16 µg/mL

D. Type of Test:

Quantitative and Qualitative growth based detection algorithm

E. Applicant:

Dade Behring

Dade MicroScan Inc.

F. Proprietary and Established Names:

MicroScan® Dried Gram-Positive MIC/Combo Panels

G. Regulatory Information:

1. Regulation section:

866.1640 Antimicrobial Susceptibility Test (AST) Powder

2. Classification:

Class II

3. Product code:

LRG-Instrument for Auto Reader & Interpretation of Overnight Antimicrobial Susceptibility Systems

JWY - Manual Antimicrobial Susceptibility Test Systems

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

83 Microbiology

H. Intended Use:

1. Intended use(s):

For use with MicroScan® Dried Gram Positive MIC/Combo, Dried Gram

Positive Breakpoint Combo and Dried Gram Positive ID Type 2 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*. Refer to Limitation of Procedure Section for use with fastidious streptococci.

2. Indication(s) for use:

The MicroScan® Dried Gram-Positive 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 gram-positive cocci. This submission is for the addition of the antibiotic daptomycin at concentrations of 0.03 - 16 µg/mL to the gram positive susceptibility panel for testing *E. faecalis* (vancomycin-susceptible and resistant strains), *E. faecium* (including vancomycin-resistant strains), *S. aureus* (including methicillin-resistant strains), *S. epidermidis* (including methicillin-resistant strains), *S. haemolyticus*, and *S. agalactiae*.

3. Special conditions for use statement(s):

For prescription use only

The Prompt® method of inoculation is an alternate method of inoculation preparation that is supported in the methodology along with the turbidity method. The stationary and log inoculum methods should not be used with this antibiotic.

The Prompt System demonstrated elevated Daptomycin MICs with staphylococci when compared with the Reference Method. If a Non-Susceptible interpretation is obtained using the Prompt System, an alternate method of obtaining a susceptible result should be used (e.g., turbidity) prior to reporting.

4. Special instrument requirements:

These panels can be read at ≥ 16 hours of incubation either manually, automatically on the autoScan® 4, or with the WalkAway® instrument systems.

I. Device Description:

The MicroScan® Dried Gram-Positive MIC/Combo Panel contains microdilutions of each antimicrobial agent in various concentrations with Mueller Hinton Broth and various nutrients which are dehydrated and dried in panels. Each panel contains two control wells: a no-growth control well (contains water only/no nutrients or broth), and a growth control well (contains test medium without antibiotic). The panel is rehydrated and inoculated at the same time with 0.1 ml of suspension prepared by the turbidity method (inoculum prepared in water, then 0.1ml transferred to 25ml of inoculum water containing pluronic-D/F-a wetting solution) for a final inoculum concentration of $3-7 \times 10^5$. The Prompt® method of inoculation is also recommended as an alternate means of preparing the inoculum. The panels are

incubated at 35° C in a non-CO₂ for 16-20 hours and read by visual observation of growth. Panels may also be read automatically with the WalkAway® or the AutoScan®4.

J. Substantial Equivalence Information:

1. Predicate device name(s):
MicroScan Dried Gram-Positive and Gram-Negative MIC/Combo Panels
2. Predicate 510(k) number(s):
K862140
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	See above	Same
Inoculum preparation	Inoculum prepared from isolated colonies using either the Turbidity method or Prompt® system	Same
Technology	Growth based after 16 hours incubation	Same
Results	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Same
Instrument	autoScan® -4 or WalkAway®	Same
Differences		
Item	Device	Predicate
Antibiotic	Daptomycin	Different concentrations depending on the antibiotic
Test organism	Gram-Positive organisms	Varies according to the antibiotic
Limitations	The performance for daptomycin has not been established with Stationary and Log Inoculum methods. Inoculum should be prepared with turbidity or Prompt® method.	None

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

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”; CLSI M7 (M100-S15) “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard”.

L. Test Principle:

After incubation in a non-CO₂ incubator for 16-20 hours, the minimum inhibitory concentration (MIC) for the test organisms are read by determining the lowest antimicrobial concentration showing inhibition of growth. The panels are read either manually using a touchScan® SR, or with the autoScan 4® or the WalkAway® instrument, which uses an optics systems with growth algorithms to directly measure organism growth.

M. Performance Characteristics (if/when applicable):**1. Analytical performance:****a. *Precision/Reproducibility:***

Reproducibility was demonstrated using 10 isolates tested at 3 sites on 3 separate days in triplicate. All ten isolates had a mode that was on scale. The mode was determined by the method used and therefore it is not always the same for each method. The study included the testing of the following inoculum and reading variables; turbidity inoculum method and Prompt® method of inoculation with reading performed manually using a touchScan® SR, autoScan 4® or the WalkAway® instrument. The following table provides the overall results for all combinations of these variables.

Difference in the number of dilutions between the mode of the MicroScan result and the actual result with each different variable for between site reproducibility						
Inoculation method	Read method	≥ Minus 2 dilutions	Minus 1 dilution	Exact	Plus 1 dilution	≥ Plus 2 dilutions
Turbidity	Manual(touchScan®)		22	218	34	
Turbidity	WalkAway ®		8	226	35	6
Turbidity	autoScan® 4	1	13	226	34	1
Prompt®	Manual(touchScan®)		53	203	19	
Prompt®	WalkAway ®		52	207	16	
Prompt®	autoScan® 4		53	207	15	

This data demonstrated very good reproducibility for each method however, it does not show if there is any difference between methods because the modes of each are used which may not be the same for each of the different read methods. For a better representation of what is going on, the Prompt® method when different is 1 more well resistant with a definite trend for the

Prompt® to be more resistant. Even though such variability between methods exists, all methods were still within the acceptable range of reproducibility.

b. Linearity/assay reportable range:

Not Applicable

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

Quality Control was performed daily with the turbidity method and with the Prompt® selectively with the following results and expected ranges as stated. The values repeat the number of times a result was obtained at each concentration.

Organism	Conc. In ug/mL	Reference result Turbidity inoc.	Turbidity inoculation with Read methods			Prompt® inoculation with Read		
			Manual	Auto-Scan®	Walk-Away®	Manual	Auto-Scan®	Walk-Away®
<i>E. faecalis</i> ATCC 29212 Exp. Range: 1 – 4 µg/mL	0.5	2				1		
	1	63	40	18	18	47	35	33
	2	108	70	59	58	61	42	44
	4							
	8							
	16							
	>16							
<i>S. aureus</i> ATCC 29213 Exp. Range: 0.25 – 1 µg/mL	0.25	164	71	49	49	12	8	9
	0.5	6	38	28	28	83	61	60
	1		1			11	6	6
<i>S. pneumoniae</i> ATCC 49619	0.12	13						
	0.25	1						
Exp. Range:								
0.06 – 0.5 µg/mL								

Quality control results demonstrated the ability of all variables of the procedure (reading and inoculation) to produce acceptable results. There appears to be a trend where the *S. aureus* was one dilution more resistant with the Prompt® inoculation method than the turbidity method. All of the Prompt® modes are 1 well more resistant than the turbidity method for the *S. aureus*. This was also observed in the reproducibility studies and the challenge study.

Inoculum density control: A turbidity meter was used for the turbidity inoculation method. The Prompt® method of inoculation had colony counts (CC) performed periodically throughout the study to determine the average inoculum density since

there is no visual check of the inoculum using this device. The Prompt® method of inoculation had far more variability with an average of 5.8×10^5 CFU/mL for *E. faecalis* with a range of 8.3×10^4 to 2.2×10^6 CFU/mL and an average of 1.82×10^6 CFU/mL for *S. aureus* with a range of 1.3×10^5 – 5.9×10^6 CFU/mL. The CFU study demonstrated that the *S. aureus* has a higher concentration of organism that reproduces a more resistant result which would explain the more resistant result with the QC, reproducibility and challenge studies. The inoculum of the Prompt® method of inoculation generally provides a higher number of CFU with more variability than a method using a turbidity meter.

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:*

Clinical testing was performed at three sites using fresh isolates supplemented with stock isolates of gram positive cocci. A comparison of the MicroScan® Dried Gram-Positive test panel results was made to the reference method as recommended in the CLSI standard M7-A6 with the following deviations from that recommendation: Pluronic-F is used as the inoculum in the frozen reference panels. This is composed of water which contains a very small amount (0.1) of Pluronic to provide a smoother draw of liquid into the inoculator. Testing of the reference method and the MicroScan panels was performed at the same time. A challenge set was also tested at one site and compared to the reference broth dilution result mode that was determined by previous testing of each isolate multiple times in the recommended reference panel. All isolates tested grew in the MicroScan panels.

Summary Table

	total	EA N	%EA	Total evaluable	EA of evaluable	%EA	CA N	%CA
Clinical	395	383	97	390	379	97.2	392	99.2
Challenge	75	73	97.3	75	73	97.3	73	97.3
Combined	470	456	97	465	452	97.2	465	98.9

EA-Essential Agreement

CA-Category Agreement

Only a susceptible category therefore there are no min, maj error vmj errors.

Evaluable results are those that fall within the test range of the reference method and could also be on-scale with the new device if within the plus/minus one well

variability. EA is when there is agreement between the reference method and the MicroScan® within plus or minus one serial two-fold dilution of antibiotic. CA is when the interpretation of the reference method agrees exactly with the interpretation of the MicroScan® result.

Five results were not in the susceptible category and CLSI's recommendation is to repeat "not susceptible" results. Out of the 5 not susceptible results, 3 were in essential agreement and repeat testing was recommended.

The challenge set of organisms was also tested using the Prompt® method and turbidity method of inoculation with all reading methods. This included seventy five challenge isolates that were tested at one site. The inoculum was prepared by the turbidity or Prompt® method and incubated in the WalkAway® instrument. All panels had additional readings performed after the WalkAway® reading was completed using the autoScan®-4 and then manually on the touchSCAN®-SR. The table below demonstrates the numbers that were in exact agreement with the reference method result and those that differed by one or more wells.

Difference in the number of dilutions between the expected reference result and the MicroScan® Result							
Inoculation method	Read method	≤ minus 2 dilutions	minus 1 dilution	Exact	Plus 1 dilution	≥ Plus 2 dilutions	% EA
Turbidity	Manual	1	11	48	14	1	97.3
Turbidity	WalkAway®	1	11	49	13	1	97.3
Turbidity	autoScan® 4	1	12	49	12	1	97.3
Prompt®	Manual		7	29	32	7	90.7
Prompt®	WalkAway®		7	33	31	4	94.7
Prompt®	autoScan® 4		7	34	31	3	96

Almost all methods had ≥95 % essential agreement except for the Prompt® method with the manual read which had an essential agreement of 90.7%. This can be attributed to the low EA with the *S. aureus* group and more results in the plus 2 dilution with the Prompt® method of inoculation. This trend to be slightly more resistant results for the Prompt® method of inoculation is consistent with the reproducibility data and also the higher CFU/ml in the Prompt® inoculum.

b. *Matrix comparison:*
Not Applicable

3. Clinical studies:

a. *Clinical Sensitivity:*
Not Applicable

b. *Clinical specificity:*
Not Applicable

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

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

Staphylococcus spp. ≤ 1 (S)

Streptococcus spp. ≤ 1 (S)

Enterococcus spp. ≤ 4 (S)

The interpretative criteria and Quality Control Ranges are the same as recommended in the FDA approved pharmaceutical package insert and the CLSI. All values are included in the package insert.

The current absence of data on resistant strains precludes defining any results other than “Susceptible”. Strains yielding MIC results suggestive of a “non-susceptible” category should be submitted to a reference laboratory for further testing.

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.