

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

A. 510(k) Number:

K062705

B. Purpose for Submission:

To add linezolid at concentrations of 0.5 to 16 µg/mL Long Dilution Sequence and 0.5 to 4 µg/mL 4-Dilution Breakpoint Sequence, for enterococci and staphylococci, to the MicroScan® Synergies plus™ Gram-Positive MIC/Combo Panels

C. Measurand:

Linezolid at 0.5 —16 µg/mL Long Dilution

Linezolid at 0.5 — 4 µg/mL 4-Dilution Breakpoint

D. Type of Test:

Quantitative and Qualitative growth based detection algorithm using optics light detection

E. Applicant:

Dade Behring Inc,
MicroScan®

F. Proprietary and Established Names:

MicroScan® Synergies plus™ Gram-Positive MIC/Combo Panels

G. Regulatory Information:

1. Regulation section:

866.1645 - Fully automated short-term incubation cycle antimicrobial susceptibility system

866.1640 - Antimicrobial Susceptibility Test Powder

2. Classification:

Class II

3. Product code:
LON – Automated AST system short incubation
LRG-Instrument for Auto Reader & Interpretation of Overnight Antimicrobial Susceptibility Systems
JWY - Manual Antimicrobial Susceptibility Test Systems
LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:
83 Microbiology

H. Intended Use:

1. Intended use(s):

For use with MicroScan® Synergies plus™ Panels read on the WalkAway® -SI System (including upgraded WalkAway® -40 or WalkAway® -96 to meet WalkAway® SI equivalence). MicroScan® panels are designed for use in determining quantitative and/or qualitative antimicrobial agent susceptibility and/or identification to the species level of colonies, grown on solid media, of rapidly growing aerobic and facultative anaerobic gram-positive cocci and *Listeria*.

2. Indication(s) for use:

The testing of Linezolid at concentrations of 0.5 –16 µg/mL to the Gram-Positive MIC/Combo test panel for testing Gram-positive enterococci and staphylococci at 4.5—16 hours or 16 –20 hours for an overnight reading. The Gram-positive organisms which may be tested on this panel are *Enterococcus faecium* (vancomycin-resistant) and *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant).

3. Special conditions for use statement(s):

Turbidity method of inoculum preparation only.
For prescription use only.

The ability of the MicroScan® Synergies plus™ Gram-Positive MIC/Combo Panels to detect resistance to Linezolid among Gram-positive isolates is unknown due to the limited number of resistant strains available at the time of comparative testing.

The current absence of data on resistant staphylococci strains precludes defining any categories other than “Susceptible”. Strains yielding results suggestive of a “nonsusceptible” category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

4. Special instrument requirements:

Not Applicable

I. Device Description:

Each panel contains two control wells: a negative control well, and a growth control well (contains test medium without antibiotic). Antibiotics are diluted in water, buffer, or

minute concentrations of broth to selected concentrations prior to dehydration of the panels.

The panel is rehydrated and inoculated at the same time with 0.1 ml of suspension prepared by the turbidity method (inoculum prepared in 0.4% saline with a very small amount (0.1%) of Pluronic®--a wetting agent, then 0.1 ml is transferred to 25ml of inoculum Synergies plus Pos Broth with Pluronic® for a final inoculum concentration of $3-7 \times 10^5$ CFU/ml.

Panels are incubated in a Walk-Away® System and read periodically starting at 4.5 hours until sufficient growth to determine the MIC (Minimum Inhibitory Concentration).

Alternately, the panels may be incubated at 35° C in a non-CO₂ for 16-24 hours and read by visual observation of growth.

J. Substantial Equivalence Information:

1. Predicate device name(s):

MicroScan® Dried Gram-Positive MIC/Combo Panels and

MicroScan® Synergies plus™ Gram-Negative MIC/Combo Panels

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

k862140

k020185

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	MicroScan® panels are designed for use in determining quantitative and/or qualitative antimicrobial agent susceptibility and/or identification to the species level of colonies, grown on solid media, of rapidly growing aerobic and facultative anaerobic organisms	Same
Specimen	Isolated colonies from culture used	Same
Inoculum	Inoculum density to 0.5 McFarland standard	Same
Incubation	<16 hours 16 – 24 hours	Same
Results	Quantitative with qualitative interpretations	Same
Technology	Growth based	Same

Differences		
Item	Device	Predicate
Panels	Dried linezolid in water	Dried clindamycin or gentamicin in broth
Reading	Uses both an early read and overnight read methods in the same system	Overnight system uses only the overnight reading method and <16 hour instruments use only the <16 hour read methods.
Inoculum preparation	Turbidity method of inoculation only.	Inoculum prepared from isolated colonies using either the Turbidity method or Prompt® system
Instrument	WalkAway® -SI System or equivalent	autoScan® -4 or WalkAway®
Antibiotic	Linezolid (0.5 – 16 µg/mL Long Dilution Sequence and 0.5 – 4 µg/mL 4-Dilution Breakpoint Sequence)	Different concentrations depending on the antibiotic

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

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”; Clinical and Laboratory Standards Institute (CLSI) M7 (M100-S16) “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard”.

L. Test Principle:

The WalkAway® SI uses a Colorimetric Optics System consisting of a color wheel/lamp assembly and a Photosensor. There is an initial read at 2.5 hours with a possible final read at 4.5, 5.5, 6.5, 8, 12, 16 or 18 hours (overnight instrument readings, manual readings), depending on the growth rate of the organism being tested. The time of final read is dependent on the user customization, the growth rate of the organism, and the sensitivity of the automatic reader since cell densities below 2×10^7 cells/ml are not detected.

M. Performance Characteristics (if/when applicable):

Data on the gram-positive panel for Linezolid at 0.5 —16 µg/mL (Long Dilution Sequence) and Linezolid at 0.5 — 4 µg/mL (4-Dilution Breakpoint Sequence) were evaluated. The Synergies plus™ readings were obtained at times between 4.5 and 16 hours of incubation (Rapid read method). An additional comparison was done with readings on the instrument after 16 – 18 hours incubation for the Overnight Instrument read method, and also for the Overnight Manual read method, when incubated 16- 18 hours and read visually.

This submission is for the AST Panel only. The ID System was not reviewed.

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility was demonstrated using 10 isolates tested at 3 sites on 3 separate days in triplicate. The study included the testing on the WalkAway® SI read at <16 hours, WalkAway® 16-18 hour readings and manual readings at 16-20 hours incubation. The overall reproducibility results were >95% reproducible for the Long Dilution Sequence and the 4-Dilution Breakpoint Sequence.

There was a slight trend for the <16 hour reading method to produce more susceptible results.

b. *Linearity/assay reportable range:*

Not Applicable

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

The recommended QC isolate was tested a sufficient number of times with acceptable results on all testing days with the reference method. The percent QC results that did not grow in the 4.5—18 hour window was 0% for the *E. faecalis* ATCC 29212 and for the *S. aureus* ATCC 29213.

Quality control results demonstrated the ability of the different reading parameters (manual and instrument) to produce acceptable results >95% of the time.

The mode for the reference method is the same as the mode produced by each reading method on the instrument.

The following table provides the frequency of the results in each concentration with the expected range stated.

Quality Control - Linezolid

Organism	Conc in µg/mL	# reference	Results		
			MicroScan®		
Linezolid Long Dilution			Manual overnight	Instrument overnight	<16 hrs instrument
<i>E. faecalis</i> ATCC 29212 Range 1 – 4 µg/mL	<=0.5				
	1				1
	2	105	112	112	111
	4		1		
	>4				

Results					
Organism	Conc in µg/mL	# reference	MicroScan®		
Linezolid Long Dilution			Manual overnight	Instrument overnight	<16 hrs instrument
<i>S. aureus</i> ATCC 29213 Range 1 – 4 µg/mL	<=0.5				
	1	1	1		
	2	92	94	101	101
	4	2	7	1	
	>4				1
Results					
Organism	Conc. in µg/mL	# reference	MicroScan®		
Linezolid 4 BP Dilutions			Manual overnight	Instrument overnight	<16 hrs instrument
<i>E. faecalis</i> ATCC 29212 Range 1 – 4 µg/mL	<=0.5				
	1				1
	2	105	112	112	111
	4		1		
	>4				
Results					
Organism	Conc. in µg/mL	# reference	MicroScan®		
Linezolid 4 BP Dilutions			Manual overnight	Instrument overnight	<16 hrs instrument
<i>S. aureus</i> ATCC 29213 Range 1 – 4 µg/mL	<=0.5				
	1	1	1		
	2	92	94	101	101
	4	2	7	1	
	>4				1

No QC trending was observed.

Inoculum density control: A turbidity meter was used for the turbidity inoculation method. Turbidity inoculum verification provided.

d. *Detection limit:*

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

The gram-positive Efficacy Study data were analyzed for both the six (6) well Long Dilution Sequence (0.5 – 16 µg/mL) and the four (4) well 4-Dilution Breakpoint Sequence (0.5 – 4 µg/mL) for enterococci and staphylococci, for which clearance is requested. The dilutions provide on-scale results for at least 1 of the CLSI gram-positive Quality Control strains. Performance claims are based on Rapid read method (<16 hours) results compared to the reference method overnight results.

a. Method comparison with predicate device:

Clinical testing was conducted at 3 sites. A total of 576 Clinical gram-positive isolates were tested of which 496 were fresh isolates and 80 were stock isolates. Seven (7) isolates for the Long Dilution Sequence and eight (8) isolates for the Breakpoint Dilution Sequence, were reported at ≥ 16 hours and were not included as Rapid read results. Therefore, of the 576 isolates tested, 568 Rapid read Long Dilution isolates were analyzed. There were 75 challenge isolates 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. One Challenge isolate reported at ≥ 16 hour and was not included in the Rapid Read Method results.

The Synergies plus™ readings were obtained at times between 4.5 and 16 hours of incubation for $> 95\%$ of the results. An additional comparison was done with readings on the instrument after overnight incubation and also read manually when incubated 16- 18 hours. Performance by these alternate reading methods was also acceptable with no apparent differences or trends.

The recommended CLSI reference method was followed with the exception of the use of a small amount (0.1%) of Pluronic® (a wetting agent) in the final inoculum. A validation of the use of Pluronic® in the frozen reference panels was conducted. Similar calculations for the different reading methods were performed with very little difference.

QC was also performed with no difference apparent in the results. The chart below demonstrates the performance of all three reading methods (Synergies plus™ readings at <16 hours, overnight on the WalkAway® and manually read at 18 hours using the touchScan®-SR) when compared to the reference method for both dilution sequences.

Clinical and Challenge Data - Read Method comparisons for Linezolid

	Total	EA	%EA	Total evaluable	EA of evaluable	%EA	CA	%CA	#R	min	maj	vmj
<16 h • Long • 4-Dil BP	643	635	98.8	602	599	99.5	638	99.2	7	2	2	1
	642	NA	NA	NA	NA	NA	637	99.2	5	2	2	1
Overnight Instrument • Long • 4-Dil BP	651	648	99.5	611	611	100.0	649	99.7	7	1	0	1
	651	NA	NA	NA	NA	NA	649	99.7	7	1	0	1
Overnight Manual • Long • 4-Dil BP	651	649	99.7	611	611	100.0	648	99.5	7	2	0	1
	651	NA	NA	NA	NA	NA	648	99.5	7	2	0	1

EA-Essential Agreement

CA-Category Agreement

R-resistant isolates

NA – Essential Agreement results are not applicable for Breakpoint format

maj-major discrepancies

vmj-very major discrepancies

min- minor discrepancies

Essential agreement (EA) is when the MicroScan® Synergies plus panel agrees with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the MicroScan® Synergies plus panel interpretation agrees exactly with the reference panel interpretation. Evaluable (Eval) are results that are within the test range and on scale.

Of the 75 Challenge isolates tested, the expected results for 72 strains were Susceptible and 3 strains were Resistant. One *Staphylococcus aureus* isolate, obtained by Microscan Technical Services from an external source, was included in the Challenge Set because it demonstrates a very rare resistance pattern to Linezolid. Further research, utilizing a national epidemiological database, revealed this resistance pattern occurrence rate for *S. aureus* against Linezolid to be <0.1%. The remaining two Linezolid resistant isolates were Other Staphylococci strains.

One (1) very major error (1/3, 33.3%) occurred in the Challenge Set data. The vmj was generated by one Other Staphylococci species for all read methods. The vmj was also generated in both the Long Dilution and the 4-Dilution Breakpoint Sequence data. The overall combined EA and the CA for the Challenge Set Data was >95% for all read methods and dilution combinations. Therefore, the Challenge Set performance data are acceptable.

Performance claims (**in bold**) that will appear in the labeling and the procedural manual are based on the Clinical data Rapid read (<16 hour) method results only. The table below displays the Clinical data results compared by reading method.

Clinical Data Read Method Comparison - Linezolid

	Total	EA	%EA	Total evaluatable	EA of evaluatable	%EA	CA	%CA	#R	min	maj	vmj
<16 h • Long • 4-Dil BP	569	564	99.1	532	531	99.8	565	99.3	4	2	2	0
	568	NA	NA	NA	NA	NA	564	99.3	2	2	2	0
Overnight Instrument • Long • 4-Dil BP	576	573	99.5	540	540	100.0	575	99.8	4	1	0	0
	576	NA	NA	NA	NA	NA	575	99.8	4	1	0	0
Overnight Manual • Long • 4-Dil BP	576	574	99.7	540	540	100.0	574	99.7	4	2	0	0
	576	NA	NA	NA	NA	NA	574	99.7	4	2	0	0

The Clinical data Rapid read method EA of 99.1% and the CA of 99.3% are both very good. Overnight Instrument and Manual read methods EA and CA are both very similar to the Rapid read method results for the Long Dilution and the 4-Dilution Breakpoint Sequence data results. There were 2 min errors (2/569, 0.4%) produced by the Rapid read and the Overnight Manual methods, and 1 min error (1/570, 0.2%) generated by the Overnight Instrument read method. There also were 2 maj errors (2/563, 0.4%) produced only by the Rapid read method.

There appears to be a trend for the device to produce a slightly more resistant result as compared to the reference method, if only by one dilution, but still remaining within EA. This trend was not observed in the reproducibility study or the QC results data.

The overall error rates are within acceptable limits for all reading methods. The performance data are acceptable for both the Long Dilution Sequence and for the 4-Dilution Breakpoint Sequence results using the Rapid read (<16 hour) method.

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 species ≤ 4 (S)

Enterococcus species ≤ 2 (S), 4 (I), ≥ 8 (R)

The interpretative criteria and Quality Control Ranges values are included in the package insert.

The current absence of data on resistant staphylococci strains precludes defining any categories other than “Susceptible”. Strains yielding results suggestive of a “nonsusceptible” category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

The ability of the MicroScan® Synergies plus™ Gram-Positive MIC/Combo Panels to detect resistance to Linezolid among Gram-positive isolates is unknown due to the limited number of resistant strains available at the time of comparative testing.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10. Performance characteristic claims that will be added to the Procedural Manual and to the labeling were based on the Clinical data Rapid read (<16 hour) method results only.

O. Conclusion:

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