

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

A. 510(k) Number:

K062938

B. Purpose for Submission:

To add nitrofurantoin at concentrations of 2 to 256 µg/mL, for enterococci and staphylococci, to the MicroScan® Synergies plus™ Gram-Positive MIC/Combo Panels

C. Measurand:

Nitrofurantoin at 2 —256 µg/mL

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 Nitrofurantoin at concentrations of 2 –256 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* species and *Staphylococcus aureus*.

3. Special conditions for use statement(s):

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

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 nitrofurantoin 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	Nitrofurantoin 2 – 256 µg/mL	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.

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M. Performance Characteristics (if/when applicable):

Data on the gram-positive panel for Nitrofurantoin at 2 – 256 µg/mL 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 all reading methods.

There was a slight trend for the <16 hr Rapid reading method to produce more susceptible results, if only by one dilution.

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

Quality Control - Nitrofurantoin

			Results		
Organism	Conc in $\mu\text{g/mL}$	# reference	MicroScan®		
Nitrofurantoin			Manual overnight	Instrument overnight	<16 hrs instrument
<i>E. faecalis</i> ATCC 29212 Range 4 – 16 $\mu\text{g/mL}$	≤ 2				
	4				
	8	42	1	2	61
	16	63	111	109	50
	32				
			Results		
Organism	Conc in $\mu\text{g/mL}$	# reference	MicroScan®		
Nitrofurantoin			Manual overnight	Instrument overnight	<16 hrs instrument
<i>S. aureus</i> ATCC 29213 Range 8 – 32 $\mu\text{g/mL}$	≤ 2				
	4				
	8	2			
	16	80	37	40	88
	32	13	63	58	11
	64			1	1

***E. faecalis* ATCC 29212 QC performance:** The mode for the reference method is the same as the mode produced by the overnight reading methods on the instrument. The Rapid read method mode is slightly more susceptible than the mode for the reference method, if only by one dilution.

***S. aureus* ATCC 29213 QC performance:** The mode for the reference method is the same as the mode produced by the Rapid reading method on the instrument.

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 Nitrofurantoin at 2 – 256 µg/mL for enterococci and staphylococci, for which clearance is requested. 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. Six (6) isolates were reported at ≥ 16 hours and were not included as Rapid read results. Therefore, of the 576 isolates tested, 570 Rapid read Long Dilution isolates were analyzed. There were 76 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.

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.

The test device had a growth rate of >95%.

Clinical and Challenge Data - Read Method comparisons for Nitrofurantoin

	Total	EA	%EA	Total evaluable	EA of evaluable	Eval %EA	CA	%CA	#R	min	maj	vmj
<16 hr Rapid	646	637	98.6	643	635	98.8	609	94.3	29	33	4	0
Overnight Instrument	652	644	98.8	648	641	98.9	633	97.1	29	16	3	0
Overnight Manual	652	648	99.4	648	645	99.5	634	97.2	29	18	0	0

EA-Essential Agreement
CA-Category Agreement
R-resistant isolates

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 76 Challenge isolates tested, the expected results for 62 strains were Susceptible, 13 strains were Intermediate, and 1 strain was Resistant. There were 11 minor errors (11/76, 14.5%) generated in the Challenge Set data, using the <16 hr Rapid reading method. All min errors were produced by *Enterococcus faecium* isolates. There were no vmj or maj, and no additional minor errors were produced in the Challenge Set using the Rapid reading method. The overall combined EA and the CA for the Clinical and Challenge Set Data were >90% for all read methods, and the overall 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 - Nitrofurantoin

	Total	EA	%EA	Total evaluable	EA of evaluable	Eval %EA	CA	%CA	#R	min	maj	vmj
<16 hr	570	563	98.8	567	561	98.9	544	95.4	28	22	4	0
Overnight Instrument	576	568	98.6	572	565	98.8	562	97.6	28	11	3	0
Overnight Manual	576	572	99.3	572	569	99.5	563	97.7	28	13	0	0

The Clinical data Rapid read method EA of 98.8% and the CA of 95.4% 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 data. There were 22 min errors (22/570, 3.9%) produced by the Rapid read method, primarily consisting of 19 one-well minor errors with *E. faecium*. This performance trend was also noted in the Challenge

Set data. The four (4) maj errors were generated by four different *Staphylococcus epidermidis* isolates among the three clinical testing sites, using the Rapid read method. The same 4 staphylococcal isolates generated three (3) maj errors using the Overnight Instrument read method. There were no vmj produced by any of the reading methods. There appears to be a trend for the device to produce a slightly more susceptible result as compared to the reference method, if only by one dilution. This trend was also observed in the reproducibility study.

The overall error rates are within acceptable limits for all reading methods. The overall combined EA and the CA for the Clinical Data were >95% for all read methods. The performance data are acceptable for the Long Dilution Sequence data 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 <=32 (S), 64 (I), >=128 (R)
Enterococcus species <=32 (S), 64 (I), >=128 (R)

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

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.