

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

A. 510(k) Number:

k111394

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Daptomycin to the MicroScan[®] MICroSTREP *plus*[®] Panel.

C. Measurand:

Daptomycin, concentrations of 0.25 – 8 µg/mL

D. Type of Test:

Antimicrobial Susceptibility Test (AST) Growth Based Detection Method

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

MicroScan[®] MICroSTREP *plus*[®] Panel

G. Regulatory Information:

1. Regulation section:

866.1640 Antimicrobial Susceptibility Test (AST) Powder

2. Classification:

II

3. Product codes:

LTT- Panels, Test, Susceptibility, Antimicrobial

LTW- Susceptibility Test Cards, Antimicrobial

JWY - Manual Antimicrobial Susceptibility Test Systems

LRG- Instrument for AutoReader & Interpretation of Overnight Susceptibility Systems

4. Panel:

83, Microbiology

H. Intended Use:

1. Intended use(s):

MICroSTREP *plus*® panels are designed for use in determining quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of aerobic streptococci, including *Streptococcus pneumoniae*.

The MicroScan® MICroSTREP *plus*® Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of aerobic streptococci. After inoculation, panels are incubated for 20 -24 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 0.25 to 8 µg/ml to the test panel.

2. Indication(s) for use:

The MicroScan® MICroSTREP *plus*® Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of aerobic streptococci. After inoculation, panels are incubated for 20 – 24 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 0.25 to 8 µg/ml to the test panel.

The organisms which may be used for Daptomycin susceptibility testing in this panel are:

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus dysgalactiae subsp. *equisimilis*.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

Manual readings and MicroScan® WalkAway® Instrument

I. Device Description:

The MicroScan® MICroSTREP plus® Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of aerobic streptococci. After inoculation, panels are incubated for 20 -24 hours at 35°C +/- 1°C in a non-CO₂ incubator, and read either visually or with MicroScan instrumentation, according to the Package insert.

Primary Read Method: Manual; Alternate Read Method: MicroScan® WalkAway System®

The MIC interpretive criteria for daptomycin are as follows:

Organism	Susceptibility Interpretive Criteria (MIC* in µg/mL):		
	S	I	R
<i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus dysgalactiae subsp. equisimilis</i>	≤ 1	-	=

*Currently there are no intermediate or resistant interpretive criteria for daptomycin. The current absence of data on daptomycin-resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding test results suggestive of a "Non-Susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

*S = Susceptible: Attainable levels in blood or tissue on usual usage, including oral administration when applicable.

I = Intermediate: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated (e.g. quinolones and B-lactams in urine), or when a higher than normal dosage of drug can be used (e.g. B-lactams). The "intermediate" category also includes a "buffer zone" which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

R = Resistant to usually achievable systemic concentrations.

J. Substantial Equivalence Information:

1. Predicate device name(s):

MicroScan MICroSTREP plus Panel – Levofloxacin

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

k020556

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Determination of susceptibility to Daptomycin with aerobic streptococci	Determination of susceptibility to Levofloxacin with aerobic streptococci including <i>S. pneumoniae</i>
Incubation Temperature	35°	Same
Inoculation	Isolated colonies from culture used	Same
Result	MIC	MIC
Incubation Atmosphere	Aerobic	Aerobic

Differences		
Item	Device	Predicate
Product Name	MicroScan MICroSTREP plus - Daptomycin	MicroScan MICroSTREP plus - Levofloxacin
Antibiotic	Daptomycin 0.25 - 8 µg/ml	Levofloxacin 0.12 - 16 µg/ml
Labeling Limitations	The current absence of resistant isolates precludes defining any category other than Susceptible. Isolates yielding MIC results suggestive of Non-susceptible category should be subjected to additional testing.	The ability of the MICroSTREP plus panel to detect resistance to Levofloxacin is unknown due to the lack of sufficient resistant strains at the time of comparative testing.
Organisms in intended use	Aerobic streptococci	Aerobic streptococci including <i>S. pneumoniae</i>

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. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacterial That Grow Aerobically, Approved Standard- 8th Edition, Document M07-A8
3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing Approved Standard-, 19th Informational Supplement, Document M100-S19

L. Test Principle:

The antimicrobial agent is diluted in water, buffer, or minute concentrations of broth to concentrations bridging the range of clinical interest. Panels are rehydrated with 115 µg Mueller-Hinton Broth supplemented with 2-5% lysed horse blood (LHB), after inoculation of the broth with a standardized suspension of the organism. After incubation in a non-CO₂ incubator for 20-24 hours, the minimum inhibitory concentration (MIC) for the test organism is manually read by visually observing the lowest antimicrobial concentration showing inhibition of growth. Alternatively, the panel can be incubated in and read by the MicroScan[®] WalkAway[®] System.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was conducted at three study sites.

Each site tested a minimum of 10 on-scale reproducibility organisms per antimicrobial agent. Selection of isolates included organisms with on-scale expected results for each antimicrobial agent included in this study. These isolates may have been selected from the challenge isolates.

Reproducibility was performed using plates with long dilution range and shortened dilution range (mapped). Because mapped dilutions have narrow range, several MIC values were off-scale. Only reproducibility calculations from the long dilution range are presented here.

Reproducibility was calculated as the percent of results for the combined sites which were within +/- one doubling dilution of the mode MIC value for all

sites. Each reproducibility organism was tested in triplicate on the dried Test panel and singly on the frozen reference panel on three different days at each site. Dried test panels were tested with the turbidity inoculation method and read manually and on the MicroScan WalkAway System.

For reproducibility calculations, off-scale values are handled in two ways; “best case” and “worst case” scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value.

The overall best case and worst case reproducibility values for manual read and WalkAway for long dilution range are shown below. These results met the acceptance criteria.

Inoculation Method	Read Method	% Reproducible (Best case-all sites)	% Reproducible (Worst case-all sites)
Turbidity	Manual	98.5	98.5
	WalkAway	97.4 (94.8)*	94.8

* Value in parentheses reflect the calculation made for off-scale values which were not included in the “Best Case” calculation because the off-scale results were several doubling dilutions from the mode and values are confirmed to be greater than one well from the mode.

b. Linearity/assay reportable range:

Not applicable

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

The recommended QC isolates were tested a sufficient number of times with acceptable results with the reference method. The MICroSTREP plus - Daptomycin test results demonstrate that the system can produce QC results in the recommended range.

Daptomycin quality control data from combined sites is shown below. For *S. pneumoniae*, the data is from 3 testing sites. QC data was analyzed for the long dilution range and shortened dilution range (mapped). At least 25 test results were available at each site. The combined QC data is shown in the following table.

QC Organism	MIC range (µg/mL)	MIC value (µg/mL)	Broth Micro Dilution Reference Frequency	Microscan Manual Read	Microscan Walk-Away Read
<i>S. pneumoniae</i> ATCC 49619	0.06 - 0.5	0.03			
		0.06	5		
		0.12	88	19	23
		0.25	17	83	79
		0.5	1	7	5
		1.0	0	2	2

All QC values were in the expected range except for two results by each reading method, which were one doubling dilution above the range. For the Manual read, 109/111 (98.2%) test results were in range and for Microscan WalkAway, 107/109 (98.2%) test results were in range. QC test results with the new device were within the expected range >95% of the time, which is acceptable.

Inoculum density checks showed acceptable results for QC organisms, as well as a select number of challenge and clinical isolates. All results were within the expected range.

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 *Streptococcus* spp. A comparison of the MICroSTREP plus - Daptomycin 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 was 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.

MicroScan MICroSTREP plus - Daptomycin and CLSI reference broth microdilution results were compared based on the guidelines provided in the AST Guidance Document. Essential agreement (EA) is when the MICroSTREP plus agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the MICroSTREP plus result interpretation agrees exactly with the reference panel result interpretation based on interpretive criteria. The %EA and %CA results were acceptable.

According to the approved drug label for daptomycin, only a susceptible interpretive category is defined. There are no intermediate or resistance interpretive categories. In this study, no isolates were noted to have MICs outside the susceptible category by the reference method. There were 2 cases in this study in which MicroScan MICroSTREP plus results gave a Daptomycin categorical interpretation that was not in agreement with the reference broth dilution MIC (Reference interpretation was “susceptible” while the MicroScan MICroSTREP plus interpretation was “non-susceptible”).

Labeling will recommend that isolates yielding a “non-susceptible” category should be submitted to a reference laboratory for further testing.

A total of 281 (214 fresh/67 stock) clinical isolates of *Streptococcus* spp. were evaluated at 3 clinical study sites. There were 107 *Streptococcus pyogenes*, 145 *Streptococcus agalactiae* and 29 other beta hemolytic streptococci belonging to Group C and Group G (*Streptococcus dysgalactiae* subsp. *equisimilis*). A total of 50 stock challenge isolates were also included and were tested at one site.

Combined results from clinical and challenge studies demonstrated an overall EA of 97% (321/331) and an overall CA of 99.3% (329/331) for the mapped (shortened) dilution range.

The performance evaluation summary of essential and category agreement results for challenge and clinical strains is shown in the tables below. Only results from manual read (primary method) are shown below for the long and short (mapped) dilution range. WalkAway read gave similar results to manual read.

Streptococci (long dilution-Manual)

Clinical data

Organism group	Total	#EA	%EA	Total	#EA of	%EA	#CA	%CA	#NS	Categorical Error (%)
	Tested		Total	Evaluable	Evaluable	Evaluable				
Other B-hemolytic Str	29	24	82.8*	29	24	82.8*	28	96.6	0	1 (3.4%)
<i>S. agalactiae</i> (Group B)	145	136	93.8	145	136	93.8	144	99.3	0	1 (0.7)
<i>S. pyogenes</i> (Group A)	107	105	98.1	107	105	98.1	107	100	0	0
Total	281	265	94.3	281	265	94.3	279	99.3	0	2 (0.7%)

Challenge

<i>S. agalactiae</i> (Group B)	19	17	89.5	19	17	89.5	19	100	0	0 (0%)
<i>S. dysgalactiae</i>	13	12	92.3	13	12	92.3	13	100	0	0 (0%)
<i>S. pyogenes</i> (Group A)	18	18	100	18	18	100	18	100	0	0 (0%)
Total	50	47	94.0	50	47	94.0	50	100	0	0 (0%)

Clinical and Challenge Combined

All Organisms	331	312	94.3	331	312	94.3	329	99.4	0	2 (0.6%)
---------------	-----	-----	------	-----	-----	------	-----	------	---	----------

*Daptomycin MIC values that were 2 doubling dilutions above the reference MIC were obtained for 5 isolates. However, this did not cause a categorical error except for 1 isolate. This data is acceptable because of the high category agreement.

Streptococci (mapped dilution-Manual)

Clinical data

Organism group	Total	#EA	%EA	Total	#EA of	%EA	#CA	%CA	#NS	Categorical Error (%)
	Tested		Total	Evaluable	Evaluable	Evaluable				
Other B-hemolytic Str	29	28	96.6	1	1	100	28	96.6	0	1 (3.4%)
<i>S. agalactiae</i> (Group B)	145	138	95.2	42	42	100	144	99.3	0	1 (0.7)
<i>S. pyogenes</i> (Group A)	107	107	100	4	4	100	107	100	0	0
Total	281	273	97.2	47	47	100	279	99.3	0	2 (0.7%)

Challenge

<i>S. agalactiae</i> (Group B)	19	17	89.5	1	1	100	19	100	0	0 (0%)
<i>S. dysgalactiae</i>	13	13	100	.	.	.	13	100	0	0 (0%)
<i>S. pyogenes</i> (Group A)	18	18	100	.	.	.	18	100	0	0 (0%)
Total	50	48	96.0	1	1	100	50	100	0	0 (0%)

Clinical and Challenge Combined

All Organisms	331	321	97.0	48	48	100	329	99.3	0	2 (0.6%)
---------------	-----	-----	------	----	----	-----	-----	------	---	----------

- 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:

*Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus dysgalactiae subsp. equisimilis are considered susceptible to daptomycin at ≤ 1 $\mu\text{g/mL}$ **

The current absence of data for resistant isolates precluded defining any results other than “susceptible”. Isolates 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 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.