510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K123933

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Ceftaroline to the MicroScan Dried Gram-Positive MIC/Combo Panel.

C. Measurand:

Ceftaroline concentrations of 0.06 – 16 µg/mL.

D. Type of Test:

Antimicrobial Susceptibility Test growth-based detection method

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

MicroScan Dried Gram-Positive MIC/Combo Panels with Ceftaroline (0.06-16 mcg/ml)

Microdilution Minimum Inhibitory Concentration (MIC) Panels

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   II

3. Product code:

   JWY – Manual Antimicrobial Susceptibility Test Systems

   LRG – Instrument for Auto reader and Interpretation of Overnight Susceptibility

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

   83, Microbiology

H. Intended Use:

1. Intended use(s):

   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 anaerobic gram-positive bacteria. 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 Ceftaroline at concentrations of 0.06 to 16 mcg/mL to the test panel.

   The gram-positive organisms which may be used for Ceftaroline susceptibility testing in this panel are:

   Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant isolates.

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 anaerobic gram-positive bacteria. After inoculation, panels are incubated for 16-20 hours at 35˚ C ± 1˚ C in a non-CO_2 incubator and read either visually or with MicroScan instrumentation, according to the Package Insert.

   This particular submission is for the addition of the antimicrobial Ceftaroline at concentrations of 0.06 to 16 mcg/mL to the test panel.

   The gram-positive organisms which may be used for Ceftaroline susceptibility testing in this panel are:

   Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant isolates.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Not Applicable

I. Device Description:

MicroScan Dried Gram-Positive MIC/Combo Panels are designed for use in determining quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram-positive bacteria.

The antimicrobial susceptibility tests are miniaturizations of the broth dilution susceptibility test that have been diluted in broth and dehydrated. Various antimicrobial agents are diluted in broth to concentrations bridging the range of clinical interest. Panels are rehydrated with water after inoculation with a standardized suspension of the organism. After incubation in a non-CO_2 incubator for 16-20 hours, the minimum inhibitory concentration (MIC) for the test organism is read by determining the lowest antimicrobial concentration showing inhibition of growth. The panels can be read manually using the MicroSCAN Microdilution Viewer or on automated MicroSCAN instrumentation (autoSCAN-4 or WalkAway systems).

Ceftaroline is a cephalosporin antibacterial agent with activity against gram-positive bacteria. The bactericidal action of Ceftaroline is mediated through binding to essential penicillin-binding proteins (PBPs). The concentrations of Ceftaroline tested in the MicroScan panel range from 0.06 µg/mL to 16 µg/mL.

Ceftaroline is indicated for treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, when caused by susceptible strains of the designated organism.

The MIC interpretive criteria for Ceftaroline are as follows:

Organism	**Susceptibility Interpretive Criteria (MIC* in µg/mL)**		
	S	**I**	**R**
Staphylococcus aureus (includes methicillin-resistant isolates)	≤ 1	-	-

Note: Clinical efficacy of Ceftaroline to treat lower respiratory infections such as community-acquired pneumonia due to methicillin-resistant *Staphylococcus*

aureus (MRSA) has not been studied in adequate and well controlled clinical trials.

[a]There are no intermediate or resistant interpretive criteria for Ceftaroline. The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

S = Susceptible; I = Intermediate; R = Resistant

J. Substantial Equivalence Information:

1. Predicate device name(s):

   MicroScan Dried Gram-Positive MIC/Combo Panels – Linezolid

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

   K003619

3. Comparison with predicate:

Similarities		
Item	Device MicroScan Dried Gram-Positive MIC/Combo Panels - Ceftaroline	Predicate MicroScan Dried Gram-Positive MIC/Combo Panels - Linezolid
Intended Use	Determination of susceptibility to Ceftaroline with gram-positive bacteria	Determination of susceptibility to Linezolid with gram-positive bacteria
Technology	Overnight microdilution MIC susceptibility tests	Same
Specimen	Isolated colonies from cultures	Same
Inoculum	Prepared using turbidity and Prompt methods	Same
Incubation Temperature	35 ˚C ± 1˚C	Same
Incubation Atmosphere	Aerobic	Same
Incubation Time	16 – 20 hours	Same
Reading Method	Automated or Manual	Same

Differences		
Item	Device	Predicate
Antibiotic	Dried Ceftaroline 0.06 – 16 µg/mL	Dried Linezolid 0.06 – 64 µg/mL

K. Standard/Guidance Document Referenced:

Guidance for Industry and FDA – Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; August 28, 2009

Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Ninth Edition. CLSI document M07-A9. 2012

L. Test Principle:

The antimicrobial susceptibility tests are miniaturizations of the broth dilution susceptibility test which have been dehydrated. Various antimicrobial agents are diluted in Mueller-Hinton broth with calcium and magnesium to concentrations bridging the range of clinical interest. After inoculation and rehydration with a standardized suspension of organism and incubation at 35˚ C for 16-20 hours, the minimum inhibitory concentration (MIC) or a qualitative susceptibility (Susceptible, Intermediate or Resistant) for the test organism is determined by observing the lowest antimicrobial concentration showing inhibition of growth.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility data for 11 *S. aureus* isolates including 5 methicillin-susceptible strains and 6 methicillin-resistant strains (10 Challenge isolates and 1 QC strain) were generated at 3 clinical trial sites. Organism selection was based on the intended use of the antimicrobic and favored strains for which the MIC was close to the breakpoints. Each strain was tested at each site in triplicate over three days using 2 inoculation methods [Turbidity and Prompt] and 3 reading methods (manual, WalkAway Instrument and autoSCAN-4 Instrument). Replicates were prepared using individually prepared inocula.

The mode of the test panel MIC results (or the median value for those results without a mode) was determined for each isolate. MIC results at each site were compared to the mode/median value. Results were considered in agreement if the test panel MIC was equal to or within ± 1 dilution of the mode/median for that isolate.

All MIC results were on-scale for both inoculation methods and all reading methods; therefore, best case and worst case scenarios were identical.

For all sites combined, results obtained with all inoculation and reading methods were ≥ 97.0%.

Reproducibility of Ceftaroline MIC testing with *S. aureus* (methicillin-susceptible and methicillin-resistant (all sites combined)

	Inoculation Method	
Reading Method	**Turbidity[a]**	**Prompt[a]**
Manual	289/297 (97.3%)	289/297 (97.3%)
WalkAway	288/297 (97.0%)	289/297 (97.3%)
autoSCAN-4	288/297 (97.0%)	289/297 (97.3%)

[a] Number (%) of results within ± 1 dilution of the mode/total number of result

The reproducibility study results are acceptable.

b. Linearity/assay reportable range:

Not applicable

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

The recommended Quality Control isolate (*S. aureus* ATCC 29213) was tested a sufficient number of times at all testing sites using both the Turbidity and Prompt inoculation methods and the three reading methods. Acceptable results (≥ 98.5 % of results within the acceptable range) as compared to the reference method were obtained for all inoculation and reading methods. The Ceftaroline test results demonstrate that the system can produce QC results within the expected range.

QC Results obtained using two inoculation methods and three read methods:

	MIC range (µg/mL)	MIC value (µg/mL)	Turbidity Inoculation Method			Prompt Inoculation Method		
			Manual Read	**WAW Read**	**AS-4 Read**	**Manual Read**	**WAW Read**	**AS-4 Read**
S. aureus ATCC 29213	0.12 – 0.5	≤ 0.06	0	0	0	0	0	0
		0.12	8	3	6	1	1	0
		0.25	95	65	62	100	67	67
		0.5	3	2	2	5	1	2
		1	1	1	1	1	1	1
		2	0	0	0	0	0	0
		4	0	0	0	0	0	0
		8	0	0	0	0	0	0
		16	0	0	0	0	0	0

WAW = WalkAway read method; AS-4 = autoSCAN-4 read method

Summary of QC results for all inoculation and read methods with *S. aureus* 29213

	Turbidity Inoculation Method			**Prompt Inoculation Method**		
	Manual Read	**WAW Read**	**AS-4 Read**	**Manual Read**	**WAW Read**	**AS-4 Read**
No (%) of test panel results in range	106/107 (99.0%)	70/71 98.5%	70/71 98.5%	106/107 99.0%	69/70 98.5%	69/70 98.5%

Growth Failure Rate: All isolates tested during the clinical (efficacy) trials grew in both the frozen reference panel and the dried MicroScan panels.

Purity check plates were performed to detect contamination during the clinical (efficacy) trials at the clinical sites. No contamination was recorded at any site.

Inoculum Density check: The MicroScan Turbidity Meter and Prompt method were used to standardize the inoculum. Turbidity meter readings were recorded each day of use. The Turbidity meter was previous cleared by FDA (K864542). Colony count validation data was reviewed and found to be acceptable.

The quality control study results are acceptable.

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:

The MicroScan Dried Gram-Positive MIC/Combo Panel with Ceftaroline results were compared to results obtained using a frozen broth microdilution panel prepared according to CLSI M07-A9 guidelines, except for the use of Pluronic-F in the inoculum water for the reference panel. All isolates were tested using the nine dilutions of Ceftaroline. Dilutions tested were appropriate for the interpretive breakpoints for the drug. For each organism tested, MIC panels were inoculated using the same standardized suspension, further diluted into 25 mL of water with either Pluronic–D (for the MicroScan dried panels) or Pluronic-F (for the frozen reference panels.) Performance was analyzed using FDA breakpoints for Ceftaroline, and results were compared based on the guidelines provided in the Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems.

A validation study was performed to demonstrate equivalence between reference panels inoculated with water supplemented with Pluronic-F and reference panels inoculated with autoclaved distilled water without Pluronic-F. The essential agreement for Pluronic-F vs. autoclaved distilled water was 100%.

A total of 306 *S. aureus* clinical isolates were tested at 3 clinical trial sites, including a total of 166 methicillin-susceptible strains, and 140 methicillin-resistant strains. Of the total, 289 isolates were fresh (less than 7 days from isolation) and 17 were stock isolates. Clinical isolates were tested using inocula prepared using the turbidity method (MicroScan Turbidity Meter) and read manually.

A total of 75 Challenge isolates were tested at one clinical trial site. Organism selection for the Challenge isolates was based on the intended use of Ceftaroline and favored strains for which the MIC was close to the breakpoint. Expected results were determined from the mode result obtained from 18

replicates of each isolate tested using a frozen reference panel prepared using CLSI M07-A9 guidelines. Challenge isolates were tested using inocula prepared using both the turbidity method and the Prompt Inoculation System. Results were read using 3 methods: manual read, WalkAway Instrument and autoSCAN-4 Instrument.

Combined results from clinical and challenge studies demonstrated an overall EA of 99.0% (377/381) and an overall CA of 99.5% (379/381) for the turbidity inoculation method with manual read.

According to the approved drug label for Ceftaroline, only a susceptible interpretive category is defined. There are no intermediate or resistant interpretive categories. In this study, there were 2 instances in which the MicroScan panel results gave a categorical interpretation for Ceftaroline that was not in agreement with the reference broth dilution MIC [reference method results were non-susceptible (MIC = 2 μg/mL), while the MicroScan results were susceptible (MIC = 1 μg/mL).] Even though the approved drug label does not define "non-susceptible" breakpoints, FDA considered this to be a potential very major error and indicative of potential "trending" at one dilution lower than expected. Recommendations were included in the labeling that isolates yielding MIC results suggestive of a non-susceptible result should be submitted to a reference laboratory for further testing. In addition, the labeling cautions users to test *S. aureus* isolates that have MICs of 1 μg/mL with an alternative testing method when indicated for patient care to reduce the risk of very major errors.

The performance evaluation summary of essential and categorical agreement results for challenge and clinical isolates is shown in the table below.

Performance of Clinical and Challenge Isolates, Turbidity Inoculation Method with Manual Read Ceftaroline

Clinical Isolates

Organism Group	Total Tested	# EA	% EA Total	Total Evaluable	# EA of Evaluable	% EA Evaluable	# CA	% CA	# NS	# vmj	# maj	# min
S. aureus MSRA	140	139	99.3	140	139	99.3	139	99.3	1	1[a]	0	0
S. aureus MSSA	166	164	98.8	163	162	99.4	166	100	0	0	0	0
Total	306	303	99.0	303	301	99.3	305	99.7	1	1[a]	0	0

Challenge Isolates

S. aureus MSRA	17	17	100	17	17	100	16	94.1	3	1[a]	0	0
S. aureus MSSA	58	57	98.3	58	57	98.3	58	100	0	0	0	0
Total	75	74	98.7	75	74	98.7	74	98.7	3	1[a]	0	0

Combined Clinical and Challenge, *S. aureus* (MRSA and MSSA)

Clinical Total	306	303	99.0	303	301	99.3	305	99.7	1	1[a]	0	0
Challenge Total	75	74	98.7	75	74	98.7	74	98.7	3	1[a]	0	0
Total Clinical and Challenge	381	377	99.0	378	375	99.2	379	99.5	4	2a	0	0

[a] There are no intermediate or resistant interpretive criteria for Ceftaroline. The current absence of resistant isolates precludes defining any results other than "Susceptible." These isolates would be considered potential very major errors (a susceptible result obtained for a non-susceptible organism

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:

Organism	**Susceptibility Interpretive Criteria (MIC in µg/mL)**		
	S	**I***	**R***
Staphylococcus aureus (includes methicillin-resistant isolates)	≤ 1	-	-

*Currently there are no intermediate or resistant interpretive criteria for Ceftaroline. The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" 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