

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

A. 510(k) Number:

k083262

B. Purpose for Submission:

Addition of Tigecycline to the MicroScan® Dried Gram-Negative MIC/Combo Panels

C. Measurand:

Tigecycline 0.015 – 32 µg/mL

D. Type of Test:

Quantitative growth based detection algorithm

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

MicroScan® Dried Gram-Negative 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 Negative MIC/Combo, Dried Gram Negative Breakpoint Combo panels. MicroScan® panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of aerobic and facultatively anaerobic gram-negative bacilli.

2. Indication(s) for use:

The MicroScan® Dried Gram-Negative 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-negative bacilli. 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 indicated for the addition of the antimicrobial Tigecycline at concentrations of 0.015 – 32 µg/mL to the gram negative susceptibility panel for testing *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae*.

3. Special conditions for use statement(s):

For prescription use only

“Do Not Report” with *Proteus mirabilis*.

The performance of Tigecycline has not been established with Stationary and Log Inoculum methods. Inoculum should be prepared with turbidity or Prompt™ method.

The ability of the MicroScan Dried Negative panels to detect resistance to Tigecycline is unknown because resistant strains were not available at the time of comparative testing.

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-Negative 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 | Determination of susceptibility to antimicrobials with gram-negative bacteria | 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 |
| Components | Dried Cefoxitin Screen Well (CfxS) 4 ug/mL | Different concentrations depending on the antibiotic |
| Test organism | Gram-Negative organisms | Varies according to the antibiotic |
| Limitations | <p>“Do Not Report” with <i>Proteus mirabilis</i>.</p> <p>The performance of Tigecycline has not been established with Stationary and Log Inoculum methods. Inoculum should be prepared with turbidity or Prompt™ method.</p> <p>The ability of the MicroScan Dried Negative panels to detect</p> | None |

| | | |
|--|---|--|
| | resistance to Tigecycline is unknown because resistant strains were not available at the time of comparative testing. | |
|--|---|--|

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-S18) “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard”.

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 supplemented with calcium and magnesium to concentrations bridging the range of clinical interest. Breakpoint Combo panels use concentrations equivalent to the categorical breakpoints of CLSI. After inoculation and rehydration with a standardized suspension of organism and incubation at 35°C for a minimum of 16 hours, the minimum inhibitory concentration (MIC) 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 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. Even though such variability between methods exists, all read methods demonstrated a reproducibility of >95%.

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®) | | 29 | 226 | 14 | 1 |

| | | | | | | |
|-----------|--------------------|--|----|-----|----|---|
| Turbidity | WalkAway® | | 35 | 229 | 5 | 1 |
| Turbidity | autoScan® 4 | | 38 | 216 | 16 | |
| Prompt® | Manual(touchScan®) | | 42 | 220 | 8 | |
| Prompt® | WalkAway® | | 32 | 228 | 10 | |
| Prompt® | autoScan® 4 | | 45 | 199 | 26 | |

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 Prompt® method with the following results and expected range 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 | Walk-Away® | Auto-Scan® | Manual | Walk-Away® | Auto-Scan® |
| | | | | | | | | |
| <i>E. coli</i> ATCC 25922 Exp. Range: 0.03 – 0.25 µg/mL | 0.06 | 52 | 23 | 4 | 34 | 17 | 5 | 27 |
| | 0.12 | 18 | 61 | 73 | 41 | 50 | 59 | 40 |
| | 0.25 | 1 | | | | 1 | 1 | 1 |
| | | | | | | | | |
| | | | | | | | | |

Quality control results demonstrated the ability of all variables of the procedure (reading and inoculation) to produce acceptable results most of the time. There appears to be a slight trend where the modes of the turbidity and Prompt® inoculation methods with the different read methods are one dilution higher compared to the mode of the reference method.

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 an average of 4.83×10^5 CFU/mL for *E. coli* ATCC 25922 with a range of 1.2×10^5 to 1.68×10^6 CFU/mL.

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 negative organisms. A comparison of the MicroScan® Dried Gram-Negative test panel results was made to the reference method as recommended in the CLSI standard M7-A7, 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.

Reference panels were made using the cation adjusted Mueller-Hinton broth and read visually after 16 – 20 hours of incubation at 35°C in a non-CO2 incubator. 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 | %EA | Total eval | EA of eval | %EA | CA | %CA | #R | min | maj | vmj |
|------------------|--------------|-----------|------------|-------------------|-------------------|------------|-----------|------------|-----------|------------|------------|------------|
| Efficacy | 307 | 303 | 98.7 | 307 | 303 | 98.7 | 304 | 99 | 0 | 3 | 0 | 0 |
| Challenge | 75 | 75 | 100 | 75 | 75 | 100 | 73 | 97.3 | 1 | 2 | 0 | 0 |
| Total | 382 | 378 | 99 | 382 | 378 | 99 | 377 | 98.7 | 1 | 5 | 0 | 0 |

EA-Essential Agreement

CA-Category Agreement

R-resistant isolates

maj-major discrepancies

vmj-very major discrepancies

min- minor discrepancies

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 dilution 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.

The challenge set of organisms was also tested using the Prompt® method and turbidity method of inoculation with all reading methods. This included 75 challenge isolates that were tested at one site. All read methods had a >95% essential agreement.

The following table demonstrates the performance based on essential agreement and category agreement for the challenge set and the different inoculation and reading methods.

| Read method | Inoculation method | No. Tested | EA N | EA% | CA N | % CA | min | maj | vmj |
|-------------|--------------------|------------|------|------|------|------|-----|-----|-----|
| Manual | Turbidity | 75 | 75 | 100 | 73 | 97.3 | 2 | 0 | 0 |
| WalkAway® | Turbidity | 75 | 75 | 100 | 70 | 93.3 | 5 | 0 | 0 |
| autoScan® 4 | Turbidity | 75 | 74 | 98.7 | 70 | 93.3 | 5 | 0 | 0 |
| Manual | Prompt® | 75 | 72 | 96 | 71 | 94.7 | 3 | 1 | 0 |
| WalkAway® | Prompt® | 75 | 72 | 96 | 72 | 96 | 2 | 1 | 0 |
| autoScan® 4 | Prompt® | 75 | 72 | 96 | 69 | 92 | 5 | 1 | 0 |

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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 dilution 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.

Overall, there appears to be a slight trend with the Efficacy study where the new device is reading more resistant than the reference method. This trend was also observed in the Challenge and QC studies.

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:

Enterobacteriaceae ≤ 2 (S), 4 (I) ≥ 8 (R)

N. Proposed Labeling:

The expected value range, interpretive criteria and QC are included in the package insert. The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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