

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

A. 510(k) Number:

K150236

B. Purpose for Submission:

To obtain a substantial equivalence determination for Dalbavancin for testing of non-fastidious organisms on the Sensititre HP MIC panel

C. Measurand:

Dalbavancin in the dilution range 0.0005 to 2 µg/mL

D. Type of Test:

Quantitative antimicrobial susceptibility test (AST), growth-based fluorescence

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

Sensititre 18-24 hour MIC or Breakpoint Susceptibility System

G. Regulatory Information:

1. Regulation section:

21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

Class II

3. Product code:

JWY – Manual Antimicrobial Test

LRG – Instrument for Autoreader and Interpretation of Overnight Susceptibility Systems

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

83, Microbiology

H. Intended Use:

1. Intended use(s):

The Sensititre 18 -24 hour MIC or Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious isolates.

2. Indication(s) for use:

The Sensititre 18 -24 hour MIC or Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious isolates.

This 510(k) is for the addition of Dalbavancin for the dilution range of 0.0005 – 2 µg/mL for testing non-fastidious gram positive organisms on the Sensititre 18- 24 hour MIC panel.

The approved primary “Indications for Use” and clinical significance for non-fastidious Gram positive isolates:

Staphylococcus aureus (including methicillin-resistant (MRSA) and methicillin susceptible (MSSA) isolates.)

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

Autoinoculator/AIM

Sensititre Vizion or AutoRead (ARIS/AutoReader OptiRead)

I. Device Description:

The Sensititre 18-24 hours MIC Breakpoint Susceptibility System is a micro-version of the classic broth dilution method and can provide both qualitative and quantitative susceptibility results in a dried microtiter plate format. Each micro-broth dilution plate is dosed with antimicrobial agents at specific dilutions and then dried.

The organism to be tested must be in pure culture and identified as *S. aureus*. A standardized suspension is prepared from colonies and inoculated into the microtiter plate using the Sensititre AutoInoculator/AIM instrument (AutoInoculator). After the indicated hours of incubation, the microtiter plate is examined for growth to determine the MIC either with the Vizion manual viewer

or using the ARIS/AutoReader/OptiRead (AutoReader). The FDA recommended interpretive criteria for Dalbavancin are listed in Table 1.

Table 1. FDA Interpretive Criteria for Dalbavancin

Organism	Susceptibility Interpretive Criteria (MIC in µg/mL)*		
	S	I	R
<i>S. aureus</i> (including methicillin-resistant isolates)	≤0.12	-	-

*The current absence of data on resistant isolates precludes defining any category other than susceptible. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Microscan Dried Gram-negative and Gram-positive MIC/Combo Panels
2. Predicate 510(k) number(s):
K010159
3. Comparison with predicate:

Table 2. Comparison with the Predicate Device

Similarities		
Item	Device K150236 Sensititre 18-24 hour Susceptibility System	Predicate K010159 Microscan Dried Gram- negative and Gram-positive MIC/Combo Panels
Intended Use	The Sensititre MIC or Breakpoint Susceptibility System is an <i>in vitro</i> diagnostic product for clinical susceptibility testing.	Microscan panels are designed for use in determining antimicrobial agent susceptibility for gram positive and gram negative isolates.
Test Panel	Each 96 well plate is precision dosed with selected antimicrobial agents and substrate for the fluorescent reads, then dried. The bacterial suspension in the	Antimicrobial agents are precision dosed into 96 wells and combined with culture media in the panel and then dried. The bacterial standardized suspension is

Similarities		
Item	Device K150236 Sensititre 18-24 hour Susceptibility System	Predicate K010159 Microscan Dried Gram- negative and Gram-positive MIC/Combo Panels
	appropriate broth is used to rehydrate the plate.	used to rehydrate the panel.
Test Organism	Non-fastidious gram positive isolates	Same
Specimen	Isolated colonies from pure culture	Same
Incubation Temperature	34-36° C	Same

Differences		
Item	Device	Predicate
Antibiotic/Assay	Dalbavancin	Gatifloxacin
Instrument	Results can be read by three different methods: 1) Automatically on an ARIS/AutoReader/Optiread using fluorescence 2) On the Vizion Device 3) Using a manual viewer, by visual reading of growth.	The Microscan Dried Gram Negative and Gram Positive MIC/Combo Panels are read visually.
Incubation	18 -24 hours	16 – 20 hours
Reading Method	Fluorescence or organism growth	Organism growth

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

M07-A9 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition, 2012

M100-S24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement, 2014

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

L. Test Principle:

Each plate (panel) is dosed with antimicrobial agents at appropriate dilutions. A standardized suspension is prepared from a pure growth of colonies and inoculated into the microtiter plate using the Sensititre AutoInoculator/AIM instrument. After the indicated hours of incubation, the microtiter plate is examined for growth to determine the MIC. Results can be read using the Vizion

reader by visual reading of growth, using a manual viewer or automatically on an AutoRead using fluorescence. The Sensititre AutoRead system utilizes fluorescence technology. The technology involves the detection of bacterial growth by monitoring the activity of specific surface enzymes produced by the test organism. Growth is determined by generating a fluorescent product from a non-fluorescent (fluorogenic) substrate. The non-fluorogenic substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The fluorophore is then said to be quenched. The plates are prepared with the substrate already added to the plate. Enzymatic action of the bacterial surface enzymes on the specific substrates cleaves this bond releasing the fluorophore, which is now capable of fluorescence. The amount of fluorescence detected is directly related to the activity of the bacterial surface enzymes and therefore, to the bacterial growth.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A reproducibility study was conducted at three sites using 25 *Staphylococcus aureus* isolates which included 13 isolates of MSSA and 12 isolates of MRSA. All isolates had on-scale MIC values. The panels were inoculated using the Autoinoculator only. Panels were read on both the Vizion and the AutoRead. The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within ± 1 dilution of the mode MIC value. The reproducibility studies for both the Vizion read method and the AutoRead method demonstrated acceptable performance of 100%.

b. *Linearity/assay reportable range:*

N/A

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

Table 3: QC Results Obtained with the Sensititre Panel Using Vizion and AutoRead Methods

QC organism	Dalbavancin MIC range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre	
				Read method	
			Manual Read	Vizion	AutoRead
<i>S. aureus</i> ATCC 29213	0.03 – 0.12	0.015	0	0	0
		0.03	30	6	5
		0.06	62	66	66
		0.12	1	19	21
		0.25	0	0	0
<i>E. faecalis</i> ATCC 29212	0.03 – 0.12	0.015	0	0	0
		0.03	17	3	3
		0.06	73	46	52
		0.12	1	42	36
		0.25	0	0	0

Growth Failure Rate: Using AutoRead, one of 161 clinical isolates (0.6%) of MSSA failed to grow in the Sensititre panels. Using Vizion read, all isolates showed sufficient growth for MIC determination.

Purity Check Plates were performed to detect contamination during the clinical testing at the clinical sites.

Inoculum Density Check: All organism suspensions were standardized spectrophotometrically. Turbidity meter readings were recorded each day of use and the inoculum density of the QC isolates were determined using traditional colony counting techniques. The mean inoculum densities for *S. aureus* were 2.7×10^5 , 2.2×10^5 , and 2.6×10^5 , for sites 1, 2 and 3, respectively, and were within the recommended ranges. The mean inoculum densities for *E. faecalis* were 2.5×10^5 , 1.6×10^5 , and 2.6×10^5 , for sites 1, 2 and 3, respectively, and were within the recommended ranges.

d. *Detection limit:*

N/A

e. *Analytical specificity:*

N/A

f. *Assay cut-off:*

N/A

2. Comparison studies:

a. *Method comparison with predicate device:*

Results obtained with the ThermoFisher Sensititre dried MIC susceptibility panels with Dalbavancin were compared to results obtained using the reference frozen broth microdilution panel (which was prepared according to CLSI M07-A9 guidelines and included 0.002% polysorbate-80). Sensititre panels were prepared using an alternative method that was developed to provide comparable results to the reference method containing polysorbate-80. The following footnote was added as a footnote to the Performance Information Tables of the device labeling:

“According to the FDA approved pharmaceutical antimicrobial agent package insert, polysorbate-80 should be used for testing freshly prepared or frozen microtiter trays with Dalbavancin. Dalbavancin on the Sensititre panel has been developed with an alternative method to provide equivalent performance to the reference method that contained polysorbate-80.”

All isolates were tested using the same 13 two-fold dilutions of Dalbavancin in both the Sensititre and in the reference panels. Dilutions tested were appropriate for the interpretive breakpoints established for the drug.

Test inocula were standardized using a spectrophotometric method; Sensititre panels were inoculated using the Autoinoculator and incubated at 34 to 36° C. Sensititre panels were read using both the Vizion and the AutoRead methods. Reference panels were inoculated as outlined in the CLSI M07-A9 document and were read manually.

The device labeling indicates that the Sensititre 18 -24 hour MIC panels can be inoculated manually or by use of the Sensititre Autoinoculator/AIM . However, the manual procedural option was not utilized for testing either the clinical isolates or the challenge isolates. Therefore, the sponsor was asked to include the following limitation in the device package insert (Technical Information):

“The performance of Dalbavancin with Streptococcus spp. was determined using the AIM autoinoculator. The use of an alternative inoculation system when testing Dalbavancin has not been evaluated.”

A total of 321 clinical isolates of *S. aureus* were tested at each of three sites, including 160 isolates of MSSA and 161 isolates of MRSA. Isolates were evaluated using AutoRead (ARIS/AutoReader OptiRead) and the Vizion. All isolates were fresh clinical isolates; no stock isolates were tested during the clinical studies. Results obtained with the Sensititre panel were compared to results obtained with a frozen reference panel (prepared using CLSI M07-A9 guidelines) performed at the clinical sites.

A total of 80 challenge isolates were tested at one site, including 40 isolates of MSSA and 40 isolates of MRSA. Isolates were tested using inocula prepared using the AutoInoculator and were read both on the Vizion and with AutoRead (ARIS/AutoReader OptiRead). Organism

selection for the challenge isolates was based on the intended use of Dalbavancin for this submission. Expected results for the challenge isolates were determined using a frozen reference panel prepared using CLSI M07-A9 guidelines.

For the Autoread result interpretation method, the combined results from clinical and challenge studies demonstrated a combined EA for *S. aureus* of 99.2% and a combined CA of 99.5%. For the Autoread interpretation method, all results were considered evaluable and therefore EA for evaluable was identical to the overall EA (Table 4). For isolates of MSSA the EA was 99.5% and the CA was 100%; for isolates of MRSA the EA was 99.0% and the CA was 99.0% (Table 5).

For the Vizion read, result interpretation method, the combined results from clinical and challenge studies demonstrated a combined EA for *S. aureus* of 99.2% and a combined CA of 99.5%. For the Vizion read interpretation method, all results were considered evaluable and therefore EA for evaluable was identical to the overall EA (Table 6). For isolates of MSSA the EA was 99.5% and the CA was 100%; for isolates of MRSA the EA was 99.0% and the CA was 99.0% (Table 7).

Six isolates of MRSA were determined to be non-susceptible to Dalbavancin by the reference method with MICs > 0.12 µg/mL. Two of the six MRSA isolates (33.3% of non-susceptible strains) were determined to be susceptible by the Sensititre panel (with MICs of 0.12 µg/mL) using both Vizion read and AutoRead. Because Dalbavancin has a defined breakpoint for susceptible and no intermediate breakpoint, these results represent potential very major errors.

However, certain considerations are given in situations in which a drug lacks an intermediate breakpoint. Because the MICs obtained with the Sensititre panels for these two strains gave MIC results that were in essential agreement with the reference method, this very major error rate was determined to be acceptable. However, users should be made aware of the possibility of very major errors when testing this drug on the Sensititre panel and should verify any Dalbavancin result ≥ 0.12 µg/mL obtained with this panel.

The sponsor was asked to include the following statement as a footnote to their Interpretation of Results table and Performance table:

*“For two strains of methicillin-resistant *S. aureus* (33.3% of non-susceptible isolates) Sensititre results were susceptible (MIC of 0.12 µg/mL) while the reference method was non-susceptible (MIC of 0.25 µg/mL). Due to a lack of an intermediate interpretation for this antimicrobial, these discrepancies are potential very major errors. Any MRSA isolate that yields MICs ≥ 0.12 µg/mL for Dalbavancin should be tested using an alternative method.”*

For the AutoRead result interpretation method, analysis of trending of MIC results (Table 8) indicated that 143 of 401 (35.7%) of *S. aureus* isolates gave Sensititre results that were more than one doubling dilution higher than the MIC determined using the reference method (containing 0.002% polysorbate-80). Similarly, using the Vizion read result interpretation method, analysis of trending of MIC results (Table 9) indicated that 170 of 401 isolates (42.6%) gave Sensititre results that were more than one doubling dilution higher than the

MIC determined using the reference method (containing 0.002% polysorbate-80). The sponsor included the following statement as a footnote to the Interpretation of Results table:

“Dalbavancin MIC values for methicillin susceptible S. aureus (MSSA) tended to be one doubling dilution higher with manual and AutoRead as compared to the reference broth microdilution method (containing 0.002% polysorbate-80). S. aureus with an interpretation of non-susceptible for Dalbavancin (>0.12 µg/mL) is uncommon in most institutions. Verify AST results if this phenotype has not been previously encountered from this patient or institution.”

The following statement was included in the Performance Table:

“Sensititre Dalbavancin MIC values for non-fastidious gram positive organisms tended to be one doubling dilution higher in S. aureus Manual and AutoRead compared to reference broth micro-dilution. S. aureus with an interpretation of non-susceptible for Dalbavancin is uncommon in most institutions or may result from technical errors. Verify AST if this phenotype has not been previously encountered from this patient or institution.”

The performance of the Sensititre panel for determination of MIC values for Dalbavancin was determined to be acceptable.

Table 4: Overall Performance of Clinical and Challenge Isolates of MSSA and MRSA, AutoRead Method

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min ^a	maj ^a	vmj ^{a,b}
Clinical	321	318	99.1	321	318	99.1	319	99.4	6	315	N/A	N/A	2 (33.3%)
Challenge	80	80	100	80	80	100	80	100	0	80	N/A	N/A	0
Combined	401	398	99.2	401	398	99.2	399	99.5	6	395	N/A	N/A	2 (33.3%)

Table 5: Performance of Clinical and Challenge Isolates by Species, AutoRead Method

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min ^a	maj ^a	vmj ^{a,b}
MSSA													
Clinical	160	159	100	160	159	100	160	100	0	160	N/A	N/A	N/A
Challenge	40	40	100	40	40	100	40	100	0	40	N/A	N/A	N/A
Combined	200	199	99.5	200	199	99.5	200	100	0	200	N/A	N/A	N/A
MRSA													
Clinical	161	159	98.8	161	159	98.8	159	98.8	6	155	N/A	N/A	2 (33.3%)
Challenge	40	40	100	40	40	100	40	100	0	40	N/A	N/A	N/A
Combined	201	199	99.0	201	199	99.0	199	99.0	6	195	N/A	N/A	2 (33.3%)

Footnotes for Tables 4 and 5:

^a There are no intermediate or resistant interpretive criteria for Dalbavancin. The current absence of resistant isolates precludes defining any results other than “Susceptible.”

^b These results would be considered potential very major discrepancies (susceptible results obtained for non-susceptible organisms)

EA = Essential Agreement
CA = Category Agreement
S = susceptible
maj = major discrepancies

Eval = Evaluable
NS = Non-susceptible
min = minor discrepancies
vmj = very major discrepancies

Table 6: Overall Performance of Clinical and Challenge Isolates, Vizion Read Method

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	No. NS	No. S	min ^a	maj ^a	vmj ^{a,b}
Clinical	321	318	99.1	321	318	99.1	319	99.4	6	315	N/A	N/A	2 (33.3%)
Challenge	80	80	100	80	80	100	80	100	0	80	N/A	N/A	N/A
Combined	401	398	99.2	401	398	99.2	399	99.5	6	395	N/A	N/A	2 (33.3%)

Table 7: Performance of Clinical and Challenge Isolates by Species, Vizion Read Method

	EA TOT	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	No. NS	No. S	min ^a	maj ^a	vmj ^{a,b}
MSSA													
Clinical	160	159	99.3	160	159	99.3	160	100	0	160	N/A	N/A	N/A
Challenge	40	40	100	40	40	100	40	100	0	40	N/A	N/A	N/A
Combined	200	199	99.5	200	199	99.5	200	100	0	200	N/A	N/A	N/A
MRSA													
Clinical	161	159	98.8	161	159	98.8	159	98.8	6	155	N/A	N/A	2 (33.3%)
Challenge	40	40	100	40	40	100	40	100	0	40	N/A	N/A	N/A
Combined	201	199	99.0	201	199	99.0	199	99.0	6	195	N/A	N/A	2 (33.3%)

Footnotes for Tables 6 and 7:

^aThere are no intermediate or resistant interpretive criteria for Dalbavancin. The current absence of resistant isolates precludes defining any results other than “Susceptible.”

^bThese results would be considered potential very major discrepancies (susceptible results obtained for non-susceptible organisms)

EA = Essential Agreement
CA = Category Agreement
S = susceptible
maj = major discrepancies

Eval = Evaluable
NS = Non-susceptible
min = minor discrepancies
vmj = very major discrepancies

Table 8. Trending of Results by AutoRead Method

Organism	No. strains	Difference in MIC as Compared to the CLSI Reference Method					
		> -2	-2	-1	0	+1	+2
MSSA	200	0	0	5 (2.5%)	122 (61.0%)	72 (36.0%)	1 (0.5%)
MRSA	201	1 (0.5%)	0	5 (2.5%)	125 (62.2%)	69 (34.3%)	1 (0.5%)
Total	401	1 (0.2%)	0	10 (2.5%)	247 (61.6%)	141 (35.2%)	2 (0.5%)

Table 9. Trending of Results by the Vizion Read Method

Organism	No. strains	Difference in MIC as Compared to the CLSI Reference Method					
		> -2	-2	-1	0	+1	+2
MSSA	200	0	0	1 (0.5%)	113 (56.0%)	85 (42.5%)	1 (0.5%)
MRSA	201	0	0	3 (1.5%)	113 (56.2%)	83 (41.3%)	1 (1.0%)
Total	401	0	0	4 (1.0%)	226 (56.4%)	168 (41.9%)	3 (0.7%)

b. *Matrix comparison:*

N/A

3. Clinical studies:

a. *Clinical Sensitivity:*

N/A

b. *Clinical specificity:*

N/A

c. Other clinical supportive data (when a. and b. are not applicable):

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

Table 10. Susceptibility Interpretive Criteria

Organism	Interpretive Criteria (Dalbavancin MIC in µg/mL)*		
	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤0.12	-	-

*The current absence of data on resistant isolates precludes defining any category other than susceptible. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional 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.