

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

A. 510(k) Number:

K143381

B. Purpose for Submission:

To obtain a substantial equivalence determination for Dalbavancin for testing of 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 *Haemophilus influenzae*/*Streptococcus pneumoniae* MIC Susceptibility Plate

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 *Haemophilus influenzae*/*Streptococcus pneumoniae* plates are *in vitro* diagnostic products for clinical susceptibility testing of *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus* species.

2. Indication(s) for use:

The Sensititre HP MIC Susceptibility plate is an *in vitro* diagnostic product for clinical susceptibility testing of fastidious isolates.

This 510(k) is for the addition of newly approved Dalbavancin for the dilution range of 0.0005 – 2 µg/mL to the Sensititre HP MIC Susceptibility plate for testing *Streptococcus* species.

The approved primary “Indications for Use” and clinical significance for *Streptococcus* spp.:

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus anginosus

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

Autoinoculator/AIM only

Sensititre Vizion or AutoRead (ARIS/AutoReader OptiRead)

I. Device Description:

The Sensititre *Haemophilus influenzae*/*Streptococcus pneumoniae* MIC Susceptibility Plate System is a micro-version of the classic broth dilutions 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 a *Streptococcus* species. 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 manually (Vizion or 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>Streptococcus agalactiae</i> , <i>Streptococcus pyogenes</i> , <i>Streptococcus anginosus</i>	≤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):
MicroSTREP Plus Panel
2. Predicate 510(k) number(s):
K021184
3. Comparison with predicate:

Table 2. Comparison with the Predicate Device

Item	Similarities	
	Device K143381 <i>Sensititre Haemophilus influenzae/Streptococcus pneumoniae</i> (HP) MIC Susceptibility Plates	Predicate K021184 MICroSTREP Plus Panel
Intended Use	<i>Sensititre Haemophilus influenzae/Streptococcus pneumoniae</i> (HP) MIC Susceptibility Plate is an <i>in vitro</i> diagnostic product for clinical susceptibility testing of <i>Haemophilus influenzae</i> ,	MICroSTREP Plus Panel is designed for use for <i>in vitro</i> clinical susceptibility testing of <i>Streptococcus</i> including <i>Streptococcus pneumoniae</i> .

Similarities		
Item	Device K143381 <i>Sensititre Haemophilus influenzae/Streptococcus pneumoniae</i> (HP) MIC Susceptibility Plates	Predicate K021184 MICroSTREP Plus Panel
	<i>Streptococcus pneumoniae</i> and <i>Streptococcus</i> species.	
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 appropriate broth is used to rehydrate the plate.	Antimicrobial agents are precision dosed into 96 wells and combined with culture media in the panel and then dried. The bacterial standardized suspension is used to rehydrate the panel.
Test Organism	<i>Streptococcus</i> spp.	<i>Streptococcus</i> spp.
Antibiotic/Assay	Dalbavancin 0.0005 to 0.2 µg/mL	Clindamycin 0.015 to 2 µg/mL
Incubation	20-24 hours	Same
Specimen	Isolated colonies from pure culture	Same
Incubation Temperature	34-36° C	Same

Differences		
Item	Device	Predicate
Instrument	Results can be read automatically on an ARIS/AutoReader/Optiread using fluorescence or manually on the Vizion or a manual viewer, by visual reading of growth.	The MICroSTREP Plus Panel is read visually.
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 manually by visual reading of growth 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 *Streptococcus* isolates which included *S. agalactiae* (13 isolates), *S. pyogenes* (11 isolates) and *S. anginosus* (1 isolate). All isolates had on-scale MIC values. The panels were inoculated using the Autoinoculator only. Panels were read both manually using the Vizion and automatically using 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 manual read method and the AutoRead method demonstrated acceptable performance of 98.7% and 100%, respectively.

b. *Linearity/assay reportable range:*

N/A

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

The FDA (and CLSI) recommended quality control isolate (*S. pneumoniae* ATCC 49619) was tested 20 times at each site using the Sensititre panels with inocula prepared using the AutoInoculator. Results were interpreted using both the manual read method (Vizion) and the AutoRead method. The QC isolate was also tested using the reference method 20 times at each site with all results falling within the acceptable range. The Dalbavancin test results demonstrate that the system can produce QC results within the expected range. However, quality control results showed clear upward trending at one doubling dilution higher than results obtained with the reference method (prepared with polysorbate-80). The FDA

recommended quality control organism, the acceptable QC range and QC results obtained with the Sensititre panel and with the reference method are listed in Table 3.

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

QC organism	Dalbavancin MIC range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre - Read method	
			Manual Read	Manual (Vizion)	AutoRead
<i>S. pneumoniae</i> ATCC 49619	0.008 – 0.03				
		0.004	0	0	0
		0.008	33 (55.0%)	1 (1.6%)	0
		0.015	21 (35.0%)	28 (46.7%)	25 (41.7%)
		0.03	6 (10.0%)	31 (51.7%)	35 (58.3%)
		0.06	0	0	0

Growth Failure Rate: Using AutoRead, seven of 418 isolates (1.7 %) failed to grow in the Sensititre panels. Using manual 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 isolate was determined using traditional colony counting techniques. The mean inoculum densities were 1.7×10^5 , 3.3×10^5 , and 2.8×10^5 , for sites 1, 2 and 3, respectively, and were within the recommended ranges.

The quality control results are acceptable.

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 to the Performance Information insert 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 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 the both the manual read method (Vizion) and the AutoRead method. Reference panels were inoculated as outlined in the CLSI M07-A9 document and were read manually.

The device labeling indicates that the *Haemophilus influenzae/Streptococcus pneumoniae* MIC panels can be manually inoculated. However, this procedural option was not utilized for testing either the clinical isolates or the challenge isolates. Therefore, the sponsor was asked to include a limitation in the device package insert stating, *“The performance of Dalbavancin with Streptococcus spp. was performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Dalbavancin has not been evaluated.”*

Clinical isolates of *Streptococcus* were tested at each of three sites. Using the AutoRead method a total of 358 *Streptococcus* clinical isolates were evaluated. The species tested included *S. agalactiae* (159 isolates), *S. pyogenes* (164 isolates) and *S. anginosus* (35 isolates). Using the manual read method, a total of 365 *Streptococcus* clinical isolates were evaluated including *S. agalactiae* (165 isolates), *S. pyogenes* (165 isolates) and *S. anginosus* (35 isolates). All isolates were fresh clinical isolates; no stock isolates were tested during the clinical studies.

A total of 60 challenge isolates were tested at one site. Isolates were tested using inocula prepared using the AutoInoculator and were read both manually and with AutoRead. Challenge isolates included *S. pyogenes* (25 isolates), *S. agalactiae* (25 isolates) and *S. anginosus* (10 isolates). 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 method, the combined results from clinical and challenge studies demonstrated an overall EA of 96.2% and an overall CA of 99.0% (See Tables 4 and 5). For the AutoRead interpretation method, all results were considered evaluable and therefore EA for evaluable was identical to the overall EA.

The data demonstrated that there was an upward trend in the MIC of the Sensititre panel compared to the reference method. Analysis of the trending of results for the AutoRead Method indicated that 78.5% of isolates gave Sensititre results that were ≥ 1 MIC doubling dilution higher than the MIC determined using the reference method (containing 0.002% polysorbate-80), with the majority of results (74.6%) at one dilution higher than the reference method (See Table 6). For most isolates the higher MIC reading did not result in a change in the categorical interpretation (susceptible vs. non-susceptible).

For the manual (VIZION) read method, the combined results from clinical and challenge studies demonstrated an overall EA of 96.7% and an overall CA of 99.1% (See Tables 7 and 8). For the manual read interpretation method, all results were considered evaluable and therefore EA for evaluable was identical to the overall EA.

Analysis of trending of results for the Manual Read Method indicated that 79.4% of isolates gave Sensititre results that were ≥ 1 MIC doubling dilution higher than the MIC determined using the reference method (containing 0.002% polysorbate-80), with the majority of results (75.8%) at one doubling dilution higher than the reference method (See Table 9). For most isolates the higher MIC reading did not result in a change in the categorical interpretation.

With both the AutoRead and manual read methods, four clinical isolates that were susceptible by the reference method (at the susceptible breakpoint of 0.12 $\mu\text{g}/\text{mL}$) gave results that were non-susceptible by Sensititre. This included one isolate each of *S. agalactiae* and *S. pyogenes* (0.6% of the susceptible clinical isolates for each species) and two isolates of *S. anginosus* (5.7% of susceptible clinical *S. anginosus* isolates). All of these four isolates had Sensititre results that were one doubling dilution higher than the reference method (reference method 0.12 $\mu\text{g}/\text{mL}$, Sensititre 0.25 $\mu\text{g}/\text{mL}$). Because the susceptible breakpoint for Dalbavancin is 0.12 $\mu\text{g}/\text{mL}$, these four isolates would be considered non-susceptible and thus, potential major errors. Because of a lack of intermediate breakpoints for this drug, this level of potential major errors was determined to be acceptable; however, users should be made aware of the possibility of categorical errors with isolates showing MIC values at the breakpoint.

The sponsor was asked to include the following statement as a footnote to their interpretation table:

“Sensititre Dalbavancin MIC values for Streptococcus species tended to be one doubling dilution higher than the reference method (containing 0.002% polysorbate-80). For one strain each of S. agalactiae (0.6% of susceptible clinical isolates) and S. pyogenes (0.6% of susceptible clinical isolates) and two strains of S. anginosus (5.7% of susceptible clinical isolates) this trending resulted in Sensititre results of non-susceptible while the reference

method results were susceptible. Due to the lack of an intermediate interpretation for this drug, this trending could result in a potential major error, especially for S. anginosus. Any Streptococcus isolates that yield MIC results $\geq 0.25 \mu\text{g/mL}$ for Dalbavancin should be submitted to a reference laboratory for additional testing."

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

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

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

Footnotes for Tables 4, 5, 7 and 8:

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

^bThese isolates would be considered potential major errors (a non-susceptible result obtained for a susceptible organism)

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

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min ^a	maj ^{a,b}	vmj ^a
Clinical	358	346	96.6	358	346	96.6	354	98.9	1	357	N/A	4 (1.1%)	0
Challenge	60	56	93.3	60	56	93.3	60	100	1	59	N/A	0	0
Combined	418	402	96.2	418	402	96.2	414	99.0	2	416	N/A	4 (1.0%)	0

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,b}	vmj ^a
<i>S. agalactiae</i>													
Clinical	159	154	96.9	159	154	96.9	158	99.4	1	158	N/A	1 (0.6%)	0
Challenge	25	23	92.0	25	23	92.0	25	100	1	24	N/A	0	0
Combined	184	177	96.2	184	177	96.2	183	99.5	2	182	N/A	1 (0.6%)	0
<i>S. pyogenes</i>													
Clinical	164	157	95.7	164	157	95.7	163	99.4	0	164	N/A	1 (0.6%)	0
Challenge	25	23	92.0	25	23	92.0	25	100	0	25	N/A	0	0
Combined	189	180	95.2	189	180	95.2	188	99.5	0	189	N/A	1 (0.5%)	0
<i>S. anginosus</i>													
Clinical	35	35	100	35	35	100	33	94.3	0	35	N/A	2 (5.7%)	0
Challenge	10	10	100	10	10	100	10	100	0	10	N/A	0	0
Combined	45	45	100	45	45	100	43	95.6	0	45	N/A	2 (4.4%)	

Table 6. Trending of Results by AutoRead Method

Organism	Difference in MIC as Compared to the CLSI Reference Method					
	-2	-1	0	+1	+2	+3
<i>S. agalactiae</i> clinical	0	0	36	118	4	1
<i>S. agalactiae</i> challenge	0	0	3	20	1	1
<i>S. pyogenes</i> clinical	0	4	29	124	5	2
<i>S. pyogenes</i> challenge	0	1	3	19	2	0
<i>S. anginosus</i> clinical	0	1	12	22	0	0
<i>S. anginosus</i> challenge	0	0	1	9	0	0
Total	0	6 (1.4%)	84 (20.1%)	312 (74.6%)	12 (2.9%)	4 (1.0%)

Table 7: Overall Performance of Clinical and Challenge Isolates, Manual 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,b}	vmj ^a
Clinical	365	353	96.7	365	353	96.7	361	98.9	1	364	N/A	4 (1.1%)	0
Challenge	60	58	96.7	60	58	96.7	60	100	1	59	N/A	0	0
Combined	425	411	96.7	425	411	96.7	421	99.1	2	423	N/A	4 (0.9%)	0

Table 8: Performance of Clinical and Challenge Isolates by Species, Manual 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,b}	vmj ^a
<i>S. agalactiae</i>													
Clinical	165	157	95.2	165	157	95.2	164	99.4	1	164	N/A	1 (0.6%)	0
Challenge	25	23	92.0	25	23	92.0	25	100	1	24	N/A	0	0
Combined	190	180	94.7	190	180	94.7	189	99.5	2	188	N/A	1 (0.5%)	0
<i>S. pyogenes</i>													
Clinical	165	161	97.6	165	161	97.6	164	99.4	0	165	N/A	1 (0.6%)	0
Challenge	25	25	100	25	25	100	25	100	0	25	N/A	0	0
Combined	190	186	97.9	190	186	97.9	189	99.5	0	190	N/A	1 (0.5%)	0
<i>S. anginosus</i>													
Clinical	35	35	100	35	35	100	33	94.3	0	35	N/A	2 (5.7%)	0
Challenge	10	10	100	10	10	100	10	100	0	10	N/A	0	0
Combined	45	45	100	45	45	100	43	95.6	0	45	N/A	2 (4.4%)	0

Table 9. Trending of Results by Manual Read Method

Organism	Difference in MIC as Compared to the CLSI Reference Method					
	-2	-1	0	+1	+2	+3
<i>S. agalactiae</i> clinical	0	0	30	127	6	2
<i>S. agalactiae</i> challenge	0	0	2	21	1	1
<i>S. pyogenes</i> clinical	0	5	30	126	3	1
<i>S. pyogenes</i> challenge	0	1	3	19	2	0
<i>S. anginosus</i> clinical	0	0	15	20	0	0
<i>S. anginosus</i> challenge	0	0	1	9	0	0
Total	0	6 (1.4%)	81 (19.0%)	322 (75.8%)	12 (2.8%)	4 (0.9%)

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>Streptococcus agalactiae</i> , <i>Streptococcus pyogenes</i> , <i>Streptococcus anginosus</i>	≤0.12	-	-

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.