



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

I Background Information:

A 510(k) Number

K242905

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Linezolid in the dilution range of 0.12-32 µg/mL

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology
LRG	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LTT	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain substantial equivalence determination for The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Linezolid in the dilution range of 0.12-32 µg/mL to expand claims to include *Streptococcus pneumoniae*, *Streptococcus* spp. β-hemolytic group, and *Streptococcus* spp. Viridans group and an expanded dilution range from 0.5-4 µg/mL from those cleared in K062783.

B Measurand:

Linezolid in the dilution range 0.12 to 32 µg/mL

C Type of Test:

Quantitative antimicrobial susceptibility test (AST) growth-based detection

III Intended Use/Indications for Use:

A 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.

B Indication(s) for Use:

The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of fastidious isolates.

This 510(k) is for linezolid in the dilution range of 0.12-32 µg/mL for testing fastidious isolates on The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System.

Linezolid has been shown to be active both clinically and *in vitro* against the following organisms according to the FDA drug label:

Streptococcus pneumoniae

Streptococcus spp. β-hemolytic group (*Streptococcus agalactiae*, *Streptococcus pyogenes*)

Linezolid has been shown to be active *in vitro* only against the following organisms according to the FDA drug label:

Streptococcus spp. Viridans group

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The following limitations were applied to linezolid testing in the appropriate sections of the device labeling that references other drugs:

Studies of the following drugs were performed with the AIM Autoinoculator. The use of an alternative inoculation system has not been evaluated.

Studies of the following drugs when tested with Streptococcus species were read using the ARIS HiQ/OptiRead and Vizion. The use of alternative read methods have not been evaluated.

To address the high potential major error rate with *S. agalactiae*, the following limitation was added to the device labeling:

Due to the occurrence of potential major errors (7/201 (3.5%)) with the ARIS/HiQ/OptiRead read method, isolates of S. agalactiae that provide Linezolid MICs of ≥ 8 $\mu\text{g/mL}$ should only be read using the Vizion read method.

To address the high potential very major error rate with *S. pyogenes*, the following limitation was added to the device labeling:

Due to the occurrence of potential very major errors (2/4 (50%)) with the ARIS HiQ/OptiRead read method, isolates of S. pyogenes tested with Linezolid should only be read using the Vizion read method.

Due to the insufficient number of non-susceptible *S. pneumoniae*, *Streptococcus* spp. β -hemolytic group, and *Streptococcus* spp. Viridans group isolates evaluated, the following limitation was applied to linezolid testing in the appropriate section of the device labeling that references other drugs:

The ability of the Sensititre system to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because an insufficient number of resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.

D Special Instrument Requirements:

Sensititre AIM for device inoculation
Sensititre Vizion digital viewing device
Sensititre ARIS HiQ/OptiRead automated plate reader

IV Device/System Characteristics:

A Device Description:

The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System is an antimicrobial susceptibility test. Each plate is dosed with antimicrobial agents at appropriate dilutions. It is a micro-version of the classic broth dilution method and can provide both qualitative and quantitative susceptibility results. After inoculation, plates are sealed with an adhesive seal, incubated at 34-36°C for 20-24 hours and examined for bacterial growth.

B Principle of Operation:

The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC Susceptibility plates are multi-well plastic microtiter plates that contain doubled dilutions of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read using the digital viewing device (Vizion) or by use of an automated plate reader (ARIS HiQ/OptiRead).

The Sensititre Vizion digital viewing device allows the panel image to be displayed on a touch screen directly from a video camera and allows the user to visually determine MIC results. The Sensititre OptiRead utilizes fluorescence technology to read the microbroth dilution plates after 20 to 24 hours incubation. 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 fluorogenic substrate. The non-fluorescent substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The enzymatic action of the bacterial surface enzymes on the bound non-fluorescent substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to the activity of bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The non-fluorescent (fluorogenic) substrate can be added to the inoculum broth which is dispensed into the test plate at the same time as the test organism, or the plates can be prepared with the substrate already added to each micro-well.

Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC plates can either be read automatically on an ARIS HiQ/OptiRead using fluorescence or by visual reading of growth on the Vizion digital viewing device.

V Substantial Equivalence Information:

A Predicate Device Name(s):

The Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Imipenem in the dilution range of 0.015-4 µg/mL.

B Predicate 510(k) Number(s):

K240445

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: <u>K242905</u>	Predicate: <u>K240445</u>
Device Trade Name	The Sensititre 20-24 hour <i>Haemophilus</i> / <i>Streptococcus pneumoniae</i> (HP) MIC or Breakpoint Susceptibility System with Linezolid in the dilution range of 0.12-32 µg/mL	The Sensititre 20-24 hour <i>Haemophilus</i> / <i>Streptococcus pneumoniae</i> (HP) MIC or Breakpoint Susceptibility System with Imipenem in the dilution range of 0.015-4 µg/mL
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Sensititre <i>Haemophilus influenzae</i> / <i>Streptococcus pneumoniae</i> plates are <i>in vitro</i> diagnostic products for clinical susceptibility testing of <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , and <i>Streptococcus species</i> .	Same

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.	Same
Incubation	20-24 hours	Same
Reading Method	Results can be read using fluorescence with the ARIS HiQ/OptiRead or by visual reading of growth with the Vizion.	Same
General Device Characteristic Differences		
Antibiotic and Dilution Range	Linezolid 0.12-32 µg/mL	Imipenem 0.015-4 µg/mL
Test Organisms	<i>Streptococcus pneumoniae</i> <i>Streptococcus</i> spp. β-hemolytic group (<i>S. agalactiae</i> , <i>S. pyogenes</i>) <i>Streptococcus</i> spp. Viridans group	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i>

VI Standards/Guidance Documents Referenced:

CLSI M07, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Eleventh Edition", (January 2018)

CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing; 33rd Edition", (March 2023)

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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study of The Sensititre 20-24-hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Linezolid was performed at three sites using a panel of sixteen (16) *Streptococcus* isolates from indicated species (6 *S. pneumoniae*, 2 *S. agalactiae*, 1 *S. pyogenes*, 1 *S. anginosus*, 1 *S. anginosus* group, 3 *S.*

sanguinis, 2 *S. salivarius*). In addition, one *S. dysgalactiae* isolate was tested that is not intended for testing with the device. All isolates were tested in triplicate over three days with each read method (i.e., automatically with the ARIS HiQ/OptiRead and visually with the Vizion). The Sensititre AIM autoinoculator was used for Sensititre plate inoculation. The mode MIC value was determined, and the reproducibility of the sixteen (16) isolates was calculated based on MIC values falling within ± 1 doubling dilution of the mode MIC value. The reproducibility studies for both the ARIS HiQ/OptiRead and Vizion read methods demonstrated acceptable performance of 100%.

2. Linearity:

Not applicable.

3. Analytical Specificity/Interference:

Not applicable.

4. Assay Reportable Range:

Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

The CLSI-recommended quality control (QC) strain *S. pneumoniae* ATCC 49619 was tested at three sites. The QC strain was tested a minimum of 20 times per site and read automatically with the ARIS HiQ/OptiRead and visually with the Vizion. The QC strain was also tested with the reference method. The results demonstrate that The Sensititre *Haemophilus influenzae*/Streptococcus pneumoniae (HP) MIC Susceptibility System with Linezolid produced quality control results within the recommended range >95% of the time (Table 1).

Table 1. Quality Control Results for *S. pneumoniae* with Linezolid with the Reference Method, ARIS HiQ/OptiRead, and Vizion

QC Organism	Expected Range (µg/mL)	Concentration (µg/mL)	Reference	ARIS HiQ/OptiRead	Vizion
<i>S. pneumoniae</i> ATCC 49619	0.25-2 µg/mL	≤0.12			
		0.25			
		0.50			
		1	68	77	70
		2	4	6	23
		≥4			

Inoculum Density: Inoculum density checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from cultures with appropriate inoculum densities were reported.

Purity Checks: Purity checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from pure cultures were reported.

Growth Failure: There were two growth failures for *S. pneumoniae*, one growth failure for *S. agalactiae*, one growth failure for *S. anginosus*, and one growth failure for *S. intermedius*.

ARIS HiQ/OptiRead Invalid (No fluorescence): There was one invalid for *S. pneumoniae*, one invalid for *S. agalactiae*, and one invalid for *S. intermedius*.

6. Detection Limit:

Not applicable

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of The Sensititre *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC Susceptibility System with Linezolid was performed at two external sites and one internal site. Results were compared to those obtained with the CLSI broth microdilution reference method. Sensititre panels were inoculated using only the AIM Autoinoculator and results were read automatically by the ARIS HiQ/OptiRead and visually by the Vizion. Reference panels were inoculated according to recommendations in the M07 CLSI document and results were interpreted manually using a mirrored reader.

No inoculation system other than the AIM Autoinoculator was used in the comparative study. To address the inoculation method limitation, the following limitation was applied to linezolid testing in the appropriate section of the device labeling that reference other drugs:

Studies of the following drugs were performed with the AIM Autoinoculator. The use of an alternative inoculation system has not been evaluated.

No read method other than ARIS HiQ/OptiRead and Vizion was used in the comparative study. To address the read method limitation, the following limitation was applied to linezolid testing in the appropriate section of the device labeling that reference other drugs:

Studies of the following drugs when tested with Streptococcus species were read using the ARIS HiQ/OptiRead and Vizion. The use of alternative read methods have not been evaluated.

The testing conditions for the reference method consisted of the following:

- Media: per CLSI M07 guidelines for *Streptococcus* spp.
- Inoculum: Inoculated per CLSI M07 guidelines
- Incubation: 34-36°C in a non-CO₂ incubator for 20 to 24 hours.

Inoculation and incubation procedure for *Streptococcus* spp.

- Media: cation-adjusted Mueller Hinton broth with TES buffer (CAMHBT) and cation-adjusted Mueller Hinton broth with TES buffer and lysed horse blood (CAMHBT+LHB)
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared with *Streptococcus* spp. in 5 mL CAMHBT. A volume of 50 µL of the standardized suspension was added to 11 mL of CAMHBT + LHB. Susceptibility panels were inoculated with 100 µL of the final organism suspension using the Sensititre AIM autoinoculator.
- Incubation: 34 - 36°C in a non-CO₂ incubator for 20 to 24 hours.

A total of 416 clinical isolates comprised of 157 *S. pneumoniae* isolates, 148 *Streptococcus* spp. β-hemolytic group isolates (74 *S. agalactiae*, 74 *S. pyogenes*), and 111 *Streptococcus* spp. Viridans group isolates (15 *S. anginosus*, 18 *S. anginosus* group (undifferentiated), 8 *S. constellatus*, 3 *S. intermedius*, 25 *S. mitis*, 13 *S. salivarius*, 11 *S. sanguinis*, 18 *Streptococcus* spp. Viridans group (undifferentiated)), as well as 188 challenge isolates comprised of 72 *S. pneumoniae* isolates, 57 *Streptococcus* spp. β-hemolytic group isolates (37 *S. agalactiae*, 20 *S. pyogenes*), and 59 *Streptococcus* spp. Viridans group isolates (25 *S. anginosus*, 5 *S. constellatus*, 5 *S. intermedius*, 9 *S. mitis*, 2 *S. oralis*, 6 *S. salivarius*, 7 *S. sanguinis*) were evaluated with the ARIS HiQ/OptiRead and the results are provided in **Table 2**.

For *S. pneumoniae* read using the ARIS HiQ/OptiRead, the combined clinical and challenge results (229 isolates) were acceptable at 98.7% and 100% for EA and CA, respectively. There were no potential major or very major errors.

For *Streptococcus* spp. β-hemolytic group read using the ARIS HiQ/OptiRead, the combined clinical and challenge results (205 isolates) were acceptable at 95.1% and 93.2% for EA and CA, respectively. There were twelve (12) potential major errors (12/201 = 6.0%) and two potential very major errors (2/4 = 50%). Since no category is defined other than “susceptible” for Linezolid for all organisms evaluated, isolates for which the MIC values are above the susceptible breakpoint are reported as non-susceptible. When categorical errors occur, these are considered potential errors. Additionally, due to the lack of a category other than “susceptible” for linezolid when testing *Streptococcus* spp. β-hemolytic group, further analysis of the errors is performed, and adjustments are made by considering the MIC values where the errors occurred. Five (5) of the twelve (12) potential major errors had an MIC value that was in essential agreement with the reference MIC value; therefore, the adjusted potential major error rate is 3.5% (7/201) and is not acceptable. The two potential very major errors had MIC values that were not in essential agreement with the reference MIC value; therefore, the adjusted potential very major error rate is 50% (2/4) and is not acceptable. When evaluating by individual species, the seven (7) adjusted potential major errors were due to *S. agalactiae* isolates, and the two (2) potential adjusted very major errors were due to *S. pyogenes* isolates. To address the high potential major error rate with *S. agalactiae*, the following limitation was added to the device labeling:

Due to the occurrence of potential major errors (7/201 (3.5%)) with the ARIS/HiQ/OptiRead read method, isolates of S. agalactiae that provide Linezolid MICs of ≥ 8 µg/mL should only be read using the Vizion read method.

To address the high potential very major error rate with *S. pyogenes*, the following limitation was added to the device labeling:

Due to the occurrence of potential very major errors (2/4 (50%)) with the ARIS HiQ/OptiRead read method, isolates of S. pyogenes tested with Linezolid should only be read using the Vizion read method.

For *Streptococcus* spp. Viridans group, read using the ARIS HiQ/OptiRead, the combined clinical and challenge results (170 isolates) were acceptable at 95.9% and 100% for EA and CA, respectively. There were no potential major or very major errors.

A limitation to address the insufficient number of non-susceptible *S. pneumoniae*, *Streptococcus* spp. β -hemolytic group, and *Streptococcus* spp. Viridans group isolates evaluated, the following limitation was applied to linezolid testing in the appropriate section of the device labeling that references other drugs:

The ability of the Sensititre system to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because an insufficient number of resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.

Table 2. Linezolid Performance of *S. pneumoniae*, *Streptococcus* spp. β -Hemolytic Group, and *Streptococcus* spp. Viridans Group Read by ARIS HiQ/OptiRead

	Total	No. EA	%EA	Eval EA Total	Eval EA No.	Eval EA %	No. CA	%CA	No. NS	No. S	min	maj	vmj
<i>S. pneumoniae</i> [≤ 2 (S)]													
Clinical	157	155	98.7	157	155	98.7	157	100	0	157	NA	0	0
Challenge	72	71	98.6	72	71	98.6	72	100	0	72	NA	0	0
Combined	229	226	98.7	229	226	98.7	229	100	0	229	NA	0	0
<i>Streptococcus</i> spp. β-hemolytic group [≤ 2 (S)]													
Clinical	148	142	96.0	148	142	96.0	142	96.0	1	147	NA	5	1
Challenge	57	53	93.0	57	53	93.0	49	86.0	3	54	NA	7	1
Combined	205	195	95.1	205	195	95.1	191	93.2	4	201	NA	12	2
<i>Streptococcus</i> spp. Viridans group [≤ 2 (S)]													
Clinical	111	105	94.6	111	105	94.6	111	100	1	110	NA	0	0
Challenge	59	58	98.3	59	58	98.3	59	100	0	59	NA	0	0
Combined	170	163	95.9	170	163	95.9	170	100	1	169	NA	0	0

NA- Not applicable

EA – Essential Agreement

CA – Categorical Agreement

S – Susceptible

NS – Non-susceptible

Maj – Major Discrepancies

EVAL – Evaluable MICs

min – Minor Discrepancies

vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

A total of 418 clinical isolates comprised of 158 *S. pneumoniae* isolates, 148 *Streptococcus* spp. β -hemolytic group isolates (74 *S. agalactiae*, 74 *S. pyogenes*), and 112 *Streptococcus* spp. Viridans group isolates (15 *S. anginosus*, 18 *S. anginosus* group (undifferentiated), 8 *S. constellatus*, 4 *S. intermedius*, 25 *S. mitis*, 13 *S. salivarius*, 11 *S. sanguinis*, 18 *Streptococcus* spp. Viridans group (undifferentiated)), as well as 188 challenge isolates comprised of 72 *S. pneumoniae* isolates, 57 *Streptococcus* spp. β -hemolytic group isolates (37 *S. agalactiae*, 20 *S. pyogenes*), and 59 *Streptococcus* spp. Viridans group isolates (25 *S. anginosus*, 5 *S. constellatus*, 5 *S. intermedius*, 9 *S. mitis*, 2 *S. oralis*, 6 *S. salivarius*, 7 *S. sanguinis*) were evaluated with the Vizion and the results are provided in **Table 3**.

For *S. pneumoniae* read using the Vizion, the combined clinical and challenge results (230 isolates) were acceptable at 99.6% and 100% for EA and CA, respectively. There were no potential major or very major errors.

For *Streptococcus* spp. β -hemolytic group read using the Vizion, the combined clinical and challenge results (205 isolates) were acceptable at 99.5% and 98.1% for EA and CA, respectively. There were no potential major errors and four (4) potential very major errors (4/4 = 100%). These are considered potential errors since no category is defined other than “susceptible.” Additionally, due to the lack of a category other than “susceptible” for linezolid when testing *Streptococcus* spp. β -hemolytic group, further analysis of the errors is performed, and adjustments are made by considering the MIC values where the errors occurred. Three (3) of the potential very major errors had MIC values that were in essential agreement with the reference MIC value; therefore, the adjusted potential very major error rate is 25% (1/4). Since it is a potential very major error due to lack of interpretive criteria other than susceptible, and the linezolid breakpoints for *Streptococcus* spp. β -hemolytic group have not changed since the most recent clearance in K062783, the performance is considered acceptable.

For *Streptococcus* spp. Viridans group, read using the Vizion, the combined clinical and challenge results (171 isolates) were acceptable at 98.8% and 100% for EA and CA, respectively. There were no potential major or very major errors.

Table 3. Linezolid Performance of *S. pneumoniae*, *Streptococcus* spp. β -Hemolytic Group, and *Streptococcus* spp. Viridans Group Read by Vizion

	Total	No. EA	%EA	Eval EA Total	Eval EA No.	Eval EA %	No. CA	%CA	No. NS	No. S	min	maj	vmj
<i>S. pneumoniae</i> [≤ 2 (S)]													
Clinical	158	157	99.4	158	157	99.4	158	100	0	158	NA	0	0
Challenge	72	72	100	72	72	100	72	100	0	72	NA	0	0
Combined	230	229	99.6	230	229	99.6	230	100	0	230	NA	0	0
<i>Streptococcus</i> spp. β-hemolytic group [≤ 2 (S)]													
Clinical	148	147	99.3	148	147	99.3	147	99.3	1	147	NA	0	1
Challenge	57	57	100	57	57	100	54	94.7	3	54	NA	0	3
Combined	205	204	99.5	205	204	99.5	201	98.1	4	201	NA	0	4
<i>Streptococcus</i> spp. Viridans group [≤ 2 (S)]													
Clinical	112	111	99.1	112	111	99.1	112	100	1	111	NA	0	0

Challenge	59	58	98.3	59	58	98.3	59	100	0	59	NA	0	0
Combined	171	169	98.8	171	169	98.8	171	100	1	170	NA	0	0

NA- Not applicable

EA – Essential Agreement

CA – Categorical Agreement

S – Susceptible

NS – Non-susceptible

Maj – Major Discrepancies

EVAL – Evaluable MICs

min – Minor Discrepancies

vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Due to the insufficient number of non-susceptible *S. pneumoniae*, *Streptococcus* spp. β -hemolytic group, and *Streptococcus* spp. Viridans group isolates evaluated, the following limitation was applied to the linezolid testing in the device labeling:

The ability of the Sensititre system to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because an insufficient number of resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.

MIC Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained for both the ARIS HiQ/OptiRead and the Vizion for *S. pneumoniae*, *Streptococcus* spp. β -hemolytic group, and *Streptococcus* spp. Viridans group. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower, at least one dilution higher, or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Species for which the difference between the percentage of isolates with higher vs. lower readings was > 30% and for which the confidence interval was determined to be statistically significant were considered to show evidence of trending. Trending that shows higher or lower MIC values compared to the reference is addressed in the labeling.

Evaluation of results for *S. pneumoniae*, *Streptococcus* spp. β -hemolytic group, and *Streptococcus* spp. Viridans group with linezolid using the ARIS HiQ/OptiRead and the Vizion are summarized in **Table 4**. A trend toward higher MIC values was observed for *S. agalactiae* using the ARIS HiQ/OptiRead when compared to the CLSI broth microdilution reference method. A trend toward lower MIC values was observed for *Streptococcus* spp. Viridans group using the ARIS HiQ/OptiRead when compared to the CLSI broth microdilution reference method. No trending was observed with the Vizion.

To address the MIC trending, the following footnotes were included in the performance table in the device labeling:

For ARIS HiQ/OptiRead:

Sensititre Linezolid MIC values tended to be in exact agreement or at least one doubling dilution higher when testing S. agalactiae with the ARIS HiQ/OptiRead compared to the CLSI reference broth microdilution method.

Sensititre Linezolid MIC values tended to be in exact agreement or at least one doubling dilution lower when testing Streptococcus spp. Viridans group with the ARIS HiQ/OptiRead compared to the CLSI reference broth microdilution method.

Table 4. Linezolid Trending Analysis for *Streptococcus pneumoniae*, *Streptococcus* spp. β -Hemolytic Group and *Streptococcus* spp. Viridans Group with ARIS HiQ/OptiRead and Vizion

Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution Lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (95% CI)	Trending Noted
ARIS HiQ/OptiRead	<i>S. pneumoniae</i>	229	40 (17.5)	171	18 (7.9)	-10%, (-16% to -4%)	No
	<i>S. agalactiae</i>	111	8 (7.2)	59	44 (39.6)	32% (22% to 42%)	Yes, high
	<i>S. pyogenes</i>	94	25 (26.6)	42	27 (28.7)	2% (-11% to 15%)	No
	<i>Streptococcus</i> spp. Viridans group	170	72 (42.4)	88	10 (5.9)	-36% (-44% to -28%)	Yes, low
Vizion	<i>S. pneumoniae</i>	230	35 (15.2)	171	24 (10.4)	-5% (-11% to -1%)	No
	<i>S. agalactiae</i>	111	8 (7.2)	84	19 (17.1)	10% (1% to 19%)	No
	<i>S. pyogenes</i>	94	37 (39.4)	41	16 (17.0)	-22% (-34% to -10%)	No
	<i>Streptococcus</i> spp. Viridans group	171	19 (11.1)	126	26 (15.2)	4% (-3% to 11%)	No

Testing/Reporting MICs for Non-indicated Species.

For this review, the interpretive criteria are applied to the organisms/organism groups according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and Cosmetic Act, the following statement is included in the Warnings and Precautions section of the device labeling to address testing and reporting of non-indicated species:

The safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.

2. Matrix Comparison:

Not applicable.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Table 5. FDA-Recognized Interpretive Criteria for Linezolid

Organisms	Minimum Inhibitory Concentrations (µg/mL) ^a		
	Susceptible	Intermediate	Resistant
<i>Streptococcus pneumoniae</i>	≤2	-	-
<i>Streptococcus</i> spp. β-hemolytic group	≤2	-	-
<i>Streptococcus</i> spp. Viridans group	≤2	-	-

^a According to the [FDA STIC Webpage](https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria)

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission incorporated by reference a breakpoint change protocol that was reviewed and accepted by FDA in submission K231994 cleared on August 25, 2023. This referenced protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (<https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria>). The referenced protocol outlined the specific procedures and acceptance criteria that Thermo Fisher Scientific intends to use to evaluate The Sensititre 20–24-hour *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Linezolid when revised breakpoints for linezolid are published on the FDA STIC

webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Thermo Fisher Scientific will update the linezolid device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.