510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K240445

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 Imipenem in the dilution range of 0.015 - 4 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 clearance for the Sensititre 20-24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Imipenem in the dilution range of 0.015-4µg/ml with FDA-recognized breakpoints for *Streptococcus pneumoniae*.

Previously obtained QC and reproducibility data with *Haemophilus influenzae* are included in this evaluation.

B Measurand:

Imipenem in the dilution range of 0.015 - 4 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* MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of fastidious isolates.

This 510(k) is for imipenem in the dilution range of 0.015 - 4 µg/ml for testing fastidious *Streptococcus pneumoniae* isolates on the Sensititre 20 – 24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System.

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

Streptococcus pneumoniae

Haemophilus influenzae

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

Bold text was used to indicate updates to the limitations to include imipenem.

The evaluation of Tedizolid and Dalbavancin, with *Streptococcus* spp. (*Streptococcus pyogenes, S. agalactiae,* and *S. anginosus*), Delafloxacin with *Streptococcus pyogenes, S. agalactiae, S. anginosus, S. pneumoniae* and *H. influenzae*, Imipenem-relebactam with *H. influenzae*, **Imipenem with *S. pneumoniae***, Ceftolozane-tazobactam with *H. influenzae*, and the evaluation of Oritavancin with *Streptococcus* spp. (*Streptococcus pyogenes, S. agalactiae, S. dysgalactiae,* and *S. anginosus*) was performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Tedizolid, Dalbavancin, Delafloxacin, Oritavancin Imipenem-Relebactam, **Imipenem**, and Ceftolozane-tazobactam has not been evaluated.

D Special Instrument Requirements:

Sensititre AIM Autoinoculator for device inoculation
Sensititre VIZION for plate reading

IV Device/System Characteristics:

A Device Description:

The device is an antimicrobial susceptibility test. Each plate is dosed with dried, stabilized 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 *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 reading device (VIZION) or by use of an automated reader (ARIS/OptiRead).

The digital reading device (VIZION) 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.

Streptococcus spp. plates can either be read automatically on an ARIS/Autoreader/OptiRead using fluorescence or by visual reading of growth on the VIZION digital viewing device.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Sensititre 20-24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint, Susceptibility System with Lefamulin in the dilution range of 0.008-16µg/mL

B Predicate 510(k) Number(s):

K193024

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K240445	Predicate: K193024
Device Trade Name	Sensititre 20-24 hour *Haemophilus / Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Imipenem in the dilution range of 0.015-4µg/mL	Sensititre 20-24 hour *Haemophilus / Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Lefamulin in the dilution range of 0.008-16µg/mL
General Device Characteristic Similarities		
Intended Use	The *Sensititre Haemophilus influenzae/Streptococcus pneumoniae* plates are *in vitro* diagnostic products for clinical susceptibility testing of *Haemophilus influenzae, Streptococcus pneumoniae* and *Streptococcus* species.	Same
Test Panel	96 well plate is 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 the ARIS HiQ/OptiRead or VIZION (digital viewing device)	1) Automatically with the OptiRead (fluorescent substrate technology) or 2) On the VIZION (digital viewing device)
Test Organisms	*Haemophilus influenzae* and *Streptococcus pneumoniae*	Same
General Device Characteristic Differences		
Antibiotic and Dilution Range	Imipenem 0.015-4µg/ml	Lefamulin 0.008-16µg/ml

VI Standards/Guidance Documents Referenced:

CLSI M7-A11: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 11th Edition

CLSI M100: Performance Standards for Antimicrobial Susceptibility Testing – 33rd Edition

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* MIC or Breakpoint Susceptibility System with Imipenem in the dilution range of 0.015-4µg/ml was previously performed in support of K912778 where 5 isolates of *Streptococcus pneumoniae* and 5 isolates of *Haemophilus influenzae* were evaluated. A supplementary reproducibility study was performed at three sites using 6 isolates of *Streptococcus pneumoniae.*

   The supplementary reproducibility study was performed at three sites using a panel of six (6) isolates of *S. pneumoniae* for a total of one hundred sixty- two (162) data points read automatically with the ARIS HiQ (OptiRead) as well as using the digital viewing/reading device (VIZION). The Sensititre AIM inoculator was used for Sensititre plate inoculation. The mode MIC value was determined, and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. Overall reproducibility was greater than 95% for *S. pneumoniae* with Imipenem. Results of this supplementary study along with the original reproducibility were considered to be acceptable.

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 quality control strain recommended by CLSI, namely *S. pneumoniae* ATCC 49619, was tested with Imipenem at three sites. The QC strain was tested a minimum of 20 times per site and read automatically with the ARIS HiQ and visually using the digital reading device (VIZION). The QC strain was also tested with the reference method. The results demonstrate that the Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC Susceptibility plates with Imipenem produced quality control results in the recommended range >95% of time (**Table 1**).

Table 1. QC Results for *S. pneumoniae* with Imipenem Compared to the Reference Method with the ARIS HiQ and the Digital Reading Device (VIZION)

QC Organism	Expected Range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre ARIS HiQ (Autoread)	Sensititre Digital Reading Device (VIZION)
S. pneumoniae ATCC 49619	0.03 – 0.12 µg/mL	≤0.0015			
		0.03	49	38	49
		0.06	19	41	30
		0.12			
		≥0.25	1	1	1

Inoculum Density: Inoculum density checks were performed for all QC, reproducibility and challenge isolates and clinical isolates tested.

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

Growth Failure: There were two growth failures for *S. pneumoniae*.

6. Detection Limit:

   Not applicable

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

The Sensititre 20-24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Imipenem in the dilution range of 0.015 - 4 µg/ml was originally cleared in K912778 with indications for testing *H. influenzae.* To evaluate the performance with *S. pneumoniae,* testing of the Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* MIC Susceptibility plates with Imipenem was performed at two external sites and one internal site. Results were compared to results obtained with the CLSI broth microdilution reference panel. Sensititre panels were inoculated using only the AIM Autoinoculator and results were interpreted using the ARIS HiQ (OptiRead) as well as using the digital viewing/reading device (VIZION) for *S. pneumoniae*. Reference panels were inoculated according to recommendations in the CLSI M07 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, an existing method limitation was modified in the device labeling to include *S. pneumoniae* with Imipenem (**modifications in bold font**):

*The evaluation of Tedizolid and Dalbavancin, with Streptococcus spp. (Streptococcus pyogenes, S. agalactiae, and S. anginosus), Delafloxacin with Streptococcus pyogenes, S. agalactiae, S. anginosus, S. pneumoniae and H. influenzae, Imipenem-relebactam with H. influenzae**, Imipenem with S. pneumoniae**, Ceftolozane-tazobactam with H. influenzae, and the evaluation of Oritavancin with Streptococcus spp. (Streptococcus pyogenes, S. agalactiae, S. dysgalactiae, and S. anginosus) was performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Tedizolid, Dalbavancin, Delafloxacin, Oritavancin Imipenem-Relebactam, **Imipenem,** and Ceftolozane-tazobactam has not been evaluated.*

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

- Media: per CLSI M07 guidelines for *S. pneumoniae*
- Inoculum: Inoculated per CLSI M07 guidelines
- Incubation: 34 - 36°C in a non-CO_2 incubator for 20 to 24 hours

S. pneumoniae

- 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, CP-114).
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared with *S. pneumoniae* in 5 mL CAMHBT. A volume of 50 µL of the standardized suspension was added to 11 mL of HTM. Susceptibility panels were inoculated with 100 µL of the final organism suspension using the Sensititre AIM.
- Incubation: 34 - 36°C in a non-CO_2 incubator for 20 to 24 hours.

A total of 155 *S. pneumoniae* clinical isolates and 72 challenge isolates were evaluated in this study. For *S. pneumoniae* read using the ARIS HiQ (OptiRead), the combined clinical and challenge results (226 isolates) was acceptable at 99.1% and 96.9% for EA and CA, respectively. There were 7 minor errors, and no major or very major errors (**Table 2)**. For *S. pneumoniae* evaluated with the digital viewing device (VIZION), the combined clinical and challenge results (227 isolates) was acceptable at 98.7% and 95.6% for EA and CA, respectively. There were 10 minor errors, and no major or very major errors (**Table 3)**.

Table 2. Imipenem Performance with Clinical and Challenge *S. pneumoniae* Isolates Read by Using the Sensititre ARIS HiQ (Autoread)

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No.S	min	maj	vmj
***S. pneumoniae* [≤ 0.12 (S), 0.25-0.5 (I), ≥1 (R)]**													
Clinical	154	153	99.4	35	34	97.1	149	96.8	3	135	5	0	0
Challenge	72	71	98.6	31	30	96.8	70	97.2	3	49	2	0	0
Total	226	224	99.1	66	64	97.0	219	96.9	6	184	7	0	0

EA – Essential Agreement
CA – Categorical Agreement
S – Susceptible
Maj – Major Discrepancies
EVAL – Evaluable MICs
R – Resistant
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.

Table 3. Imipenem Performance with Clinical and Challenge *S. pneumoniae* Isolates Read by Using the Digital Viewing Device (VIZION).

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No.S	min	maj	vmj
***S. pneumoniae* [≤ 0.12 (S), 0.25-0.5 (I), ≥1 (R)]**													
Clinical	155	153	98.7	36	34	94.4	149	96.1	3	136	6	0	0
Challenge	72	71	98.6	31	30	96.8	68	94.4	3	49	4	0	0
Total	227	224	98.7	67	64	95.5	217	95.6	6	185	10	0	0

EA – Essential Agreement
CA – Categorical Agreement
S – Susceptible
Maj – Major Discrepancies
EVAL – Evaluable MICs
R – Resistant
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.

Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained for both the ARIS HiQ (OptiRead) and the digital viewing device (VIZION) for *S. pneumoniae*. 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* and Imipenem using either the autoread method (ARIS HiQ) and the digital viewing device (VIZION) did not indicate trending for *S. pneumoniae*.

Table 4. Trending Analysis for *S. pneumoniae* with Imipenem Using the Sensititre ARIS HiQ (Autoread)

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
S. pneumoniae	226	6 (2.7%)	203 (89.8%)	17 (7.5%)	4.9% (0.8% to 9.3%)	No

Table 5. Trending Analysis for *S. pneumoniae* with Imipenem Read by Using the Digital Viewing Device (VIZION)

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
S. pneumoniae	227	5 (2.2%)	192 (84.6%)	30 (13.2%)	11.0% (6.3% to 16.2%)	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 6. FDA-Recognized Interpretive Criteria for Imipenem

Organism	Interpretive Criteria for Imipenem		
	Susceptible	Intermediate	Resistant
S. pneumoniae	≤0.12	0.25-0.5	≥1

[a]According to the FDA STIC Webpage

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/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The referenced protocol outlined the specific procedures and acceptance criteria that Thermo Fisher intends to use to evaluate the Sensititre 20–24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Imipenem when revised breakpoints for Imipenem are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Thermo Fisher will update the Imipenem 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.