510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K230935

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

Sensititre 20-24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC, or Breakpoint Susceptibility System with Imipenem-relebactam in the dilution, range of 0.03/4-128-4ug/ml (*Haemophilus influenzae*)

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 a substantial equivalence for the addition of *Haemophilus influenzae* for testing with Imipenem-relebactam on the Sensititre 20-24-Hour MIC *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Imipenem-relebactam in the dilution range of 0.03/4 – 128/4 µg/ml

B Measurand:

Imipenem-relebactam 0.03/4 – 128/4 µg/ml

C Type of Test:
Quantitative Antimicrobial Susceptibility Test (AST) growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

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

This 510(k) is for Imipenem-relebactam in the dilution range of 0.03/4–128/4 µg/ml for testing *H. influenzae* on the Sensititre 20 - 24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System.

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

Haemophilus influenzae

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

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*, 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, Imipenem-relebactam and Oritavancin has not been evaluated.

The performance of Imipenem-relebactam was determined using the digital reading device (VIZION) reading method only. The use of an alternative reading method when testing Imipenem-relebactam has not been evaluated.

The ability of Sensititre to detect non-susceptibility of *H.influenzae* to imipenem-relebactam has not been established due to an insufficient number of non- susceptible isolates encountered at the time of comparative testing.

Due to a lack of interpretive criteria other than susceptible, isolates of *H. influenzae* yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

D Special Instrument Requirements:
Sensititre AIM for device inoculation
Digital reading device Sensititre VIZION

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 manually select 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 pneumoniae and *Streptococcus* spp. plates can either be read on the digital reading device (VIZION) or automatically on the Sensititre ARIS/OptiRead. *H. influenza* can only be read on the digital reading device (VIZION).

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 0.008-16ug/mL

B Predicate 510(k) Number(s):

K193024

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K230935	Predicate: K193024
Device Trade Name	Sensititre 20-24 hour *Haemophilus / Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Imipenem-relebactam in the dilution range of 0.03/4- 128/4µg/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/Indications For Use	Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC Susceptibility plate is an in vitro diagnostic product 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	
Incubation	20-24 hours	Same
Reading method	Manual	Same
General Device Characteristic Differences		
Test Organisms	*Haemophilus influenzae*	*Haemophilus influenzae* and *Streptococcus* spp.
Antibiotic and Dilution Range	Imipenem-relebactam 0.03/4-128/4µg/ml	Lefamulin 0.008-16µg/ml

VI Standards/Guidance Documents Referenced:

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

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

CLSI M100-ED32: Performance Standards for Antimicrobial Susceptibility Testing; Approved Standard – 32nd Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study was performed at four sites using a panel of ten isolates of *H. influenzae* for a total of 360 data points read using the digital viewing 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. Reproducibility was greater than 95% for *H. influenzae* read using the digital reading device (VIZION). Results 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 was tested with Imipenem-relebactam at four sites using *H. influenzae* ATCC 49766. The QC strain was tested a minimum of 20 times per site and read 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-relebactam produced quality control results in the recommended range >95% of time (**Table 1**).

Table 1. QC Results for *H. influenzae* with Imipenem-relebactam with the Reference Method and the Digital Reading Device (Vizion)

QC Organism	Expected Range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre Digital Reading Device (VIZION)
H. influenzae ATCC 49766	0.25/4 – 1/4 µg/mL	0.12/4	-	-
		0.25/4	17	3
		0.5/4	64	76
		1/4	1	2
		2/4	-	-

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 no growth failures for *H. influenzae.*

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* MIC Susceptibility plates with Imipenem-relebactam was performed at three 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 only the digital reading device (VIZION) for *H. influenzae*. 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 sponsor modified the existing method limitation in the device labeling to include *H. influenzae* with Imipenem-relebactam (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****, 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****, Imipenem-relebactam*** *and Oritavancin has not been evaluated.*

No reading method other than the digital reading device (VIZION) was used in the comparative study. To address the read methods limitation, the sponsor added the read method limitation in the device labeling:

> *The performance of Imipenem-relebactam was determined using the digital reading device (VIZION) reading method only. The use of an alternative reading method when testing Imipenem-relebactam has not been evaluated.*

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

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

H. influenzae

- Media: CAMHBT and Haemophilus Test Medium (HTM)
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared with *H. influenzae* 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 393 *H. influenzae* clinical isolates and 50 *H. influenzae* challenge isolates were evaluated. For *H. influenzae* read using the digital reading device (VIZION), the combined clinical and challenge results (443 isolates) were acceptable at 94.1% and 99.3% for EA and CA, respectively. There were potential three major errors (3/440 = 0.7%) and no very major errors **(Table 2).**

Because only three non-susceptible isolates of *H. influenzae* were evaluated, the following limitation was included in the device labeling:

> *The ability of Sensititre to detect non-susceptibility of H. influenzae to Imipenem-relebactam has not been established due to an insufficient number of non-susceptible isolates encountered at the time of comparative testing.*

The FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria webpage (STIC) indicates that the current absence of resistant isolates precludes defining any results for delafloxacin testing with *H. influenzae* other than "susceptible." To address the inclusion of only a susceptible breakpoint, the sponsor included the following limitation:

> *Due to a lack of interpretive criteria other than susceptible for Imipenem-relebactam, isolates of H. influenzae yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.*

Table 2. Imipenem-relebactam results for *H. influenzae* with Digital Reading Device (VIZION)

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
***H. influenza* (Susceptible ≤ 4/4 µg/mL)**													
Clinical	393	370	94.1	390	367	94.1	390	99.2	3	390	0	3	0
Challenge	50	47	94.0	49	46	94.0	50	100	0	50	0	0	0
Total	443	417	94.1	439	413	94.1	440	99.3	3	440	0	3	0

EA – Essential Agreement (± 1 doubling dilution)
CA – Categorical Agreement
S – Susceptible
Maj – Major Discrepancies
EVAL – Evaluable MICs
NS – Non-Susceptible
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 results 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 the VIZION read method for *H. influenzae*. 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 *H. influenzae* and Imipenem-relebactam using the digital reading device (VIZION) did not indicate trending **(Table 3)**.

Table 3. Trending Observed by VIZION read method for *H. influenzae* with Imipenem-relebactam.

Organism/Read Method	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
H. influenzae /digital reading device (VIZION) Read	440	85 (19.3)	201 (45.7)	154 (35.0)	15% (9.8% to 21.4%)	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 4. FDA-Identified Interpretive Criteria for Imipenem-Relebactam

Organism	Interpretive Criteria for Imipenem-relebactam[a]		
	Susceptible	Intermediate	Resistant
H. influenzae	≤4/4	-	-

[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 included a breakpoint change protocol that was reviewed and accepted by FDA. This 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 protocol outlined the specific procedures and acceptance criteria that ThermoFisher intends to use to evaluate the Sensititre 20–24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Imipenem-relebactam when revised breakpoints for Imipenem-Relebactam are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, ThermoFisher will update the Imipenem-Relebactam 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.