510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K232310

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Ceftolozane-tazobactam in the dilution range of 0.03/4-64/4ug/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 a substantial equivalence determination for the addition of Ceftolozane-tazobactam on the Sensititre 20-24-Hour MIC *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System

B Measurand:

Ceftolozane-tazobactam 0.03/4 - 64/4 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 diagnositic product for clinical susceptibility testing of fastidious isolates.

This 510(k) is for Ceftolozane-tazobactam in the dilution range of 0.03/4 - 64/4 µg/ml for testing *H. influenzae* on the Sensititre 20 - 24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System.

Ceftolozane-tazobactam 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

Bold text was used to indicate updates to the limitations to include ceftolozane-tazobactam.

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*, **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, and **Ceftolozane-tazobactam** has not been evaluated.

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

Due to a lack of interpretive criteria other than susceptible for Ceftolozane-tazobactam, 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
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* 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. influenzae* 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:** K232310	**Predicate:** K193024
Device Trade Name	Sensititre 20-24 hour *Haemophilus / Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Ceftolozane-tazobactam in the dilution range of 0.03/4 - 64/4 µg/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 VIZION (digital viewing device) only	Same
General Device Characteristic Differences		
Test Organisms	*Haemophilus influenzae*	*Haemophilus influenzae* and *Streptococcus* spp.

Device & Predicate Device(s):	Device: K232310	Predicate: K193024
Antibiotic and Dilution Range	Ceftolozane-tazobactam 0.03/4 - 64/4 µg/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-S26: Performance Standards for Antimicrobial Susceptibility Testing; Approved Standard – 26th Informational Supplement

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study was performed at three sites using a panel of twenty-five (25) isolates of *H. influenzae* for a total of seventy-five (75) 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 97% for *H. influenzae* read using the digital reading device (VIZION) with Ceftolozane-tazobactam. 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, namely *H. influenzae* ATCC 49247, was tested with Ceftolozane-tazobactam at three sites. 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 Ceftolozane-tazobactam produced quality control results in the recommended range >95% of time (**Table 1**).

Table 1. QC Results for *H. influenzae* with Ceftolozane-tazobactam 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 49247	0.5/4 – 2/4 µg/mL	0.25/4	-	-
		0.5/4	3	17
		1/4	50	39
		2/4	7	4
		4/4	-	-

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 Ceftolozane-tazobactam 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 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 Ceftolozane-tazobactam (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, ***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,* ***and Ceftolozane-tazobactam*** *has not been evaluated.*

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

The performance of Ceftolozane-tazobactam for H. influenzae was determined using the VIZION reading method only. The use of an alternative reading method when testing Ceftolozane-tazobactam 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 05 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 248 *H. influenzae* clinical isolates and 50 *H. influenzae* challenge isolates were evaluated. The sponsor evaluated 288 susceptible organisms and 10 non-susceptible organisms. For *H. influenzae* read using the digital reading device (VIZION), the combined clinical and challenge results (298 isolates) were acceptable at 97.7% and 99.3% for EA and CA, respectively. There was one potential major error (1/288 = 0.3%) and one potential very major error (1/10 = 10%).

Due to the lack of an intermediate interpretive criterion (ceftolozane-tazobactam only has a "susceptible" category), further analysis of the categorical errors was performed and adjustments made by considering the MIC values where the errors occurred. The potential very major error was one doubling dilution from the reference and thus in essential agreement. Therefore, the adjusted very major error rate is 0% (0/10), which is acceptable. To address the adjustment of the potential very major error, the following performance footnote was included in the device labeling:

"*The overall potential very major error rate for Ceftolozane-tazobactam when testing H. influenzae clinical and challenge isolates is 10% (1/10). Based on the essential agreement and lack of an intermediate breakpoint for Ceftolozane-tazobactam, the overall adjusted potential very major error rate for H. influenzae clinical and challenge isolates is 0% (0/10).*"

To address the susceptible-only breakpoint for ceftolozane-tazobactam, the following limitation was included in the device labeling:

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

Table 2. Ceftolozane-tazobactam Performance with Clinical and Challenge *H. influenzae* Isolates

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
***H. influenza* (Susceptible ≤ 0.5/4 µg/mL)**													
Clinical	248	241	97.2	238	231	97.1	247	99.6	10	238	-	0	1
Challenge	50	50	100	46	46	100	49	98.0	0	50	-	1	0
Total	298	291	97.7	284	277	97.5	296	99.3	10	288	-	1	1

EA – Essential Agreement
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 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 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 Ceftolozane-tazobactam using the digital reading device (VIZION) did not indicate trending.

Table 3. Trending Analysis for *H. influenzae* with Ceftolozane-tazobactam

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
H. influenzae	289	16 (5.5)	179 (62.0)	94 (32.5)	27.0% (21% to 33%)	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 Ceftolozane-tazobactam

Organism	Interpretive Criteria for Ceftolozane-tazobactam[a]		
	Susceptible	Intermediate	Resistant
H. influenzae	≤0.5/4	-	-

[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 Ceftolozane-tazobactam when revised breakpoints for Ceftolozane-tazobactam 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 Ceftolozane-tazobactam 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.