510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

I Background Information:

A 510(k) Number
K223844

B Applicant
Thermo Fisher Scientific

C Proprietary and Established Names
Sensititre 20–24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.00025-8µg/ml (*Streptococcus pneumoniae*) and 0.000125-8µg/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

II Submission/Device Overview:

A Purpose for Submission:
To obtain a substantial equivalence for the addition of *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates recovered from Community Acquired Bacterial Pneumonia (CABP) for testing with delafloxacin on the Sensititre 20-24-hour MIC *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.00025-8µg/ml (*S. pneumoniae*) and 0.000125-8µg/ml (*H. influenzae*) using panels each with the appropriate media.

B Measurand:

Delafloxacin – *Streptococcus* spp. and *Streptococcus pneumoniae* 0.00025 – 8µg/mL
Delafloxacin – *Haemophilus influenza* 0.000125 – 8µg/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 delafloxacin in the dilution range of 0.00025-8 µg/ml for testing fastidious *Streptococcus* spp., (including *S. pneumoniae*) and delafloxacin in the dilution range of 0.000125 - 8 µg/mL for testing *H. influenzae* on the Sensititre 20 - 24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System.

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

For Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus anginosus grp.

For Community Acquired Bacterial Pneumoniae (CABP)

Streptococcus pneumoniae
Haemophilus influenzae

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Limitations
AST testing of Delafloxacin with *S. pneumoniae* and read using the digital viewing device (VIZION) and ARIS/OptiRead was performed using cation-adjusted Mueller Hinton broth with TES buffer and lysed horse blood (CAMHBT+LHB, CP-114)

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* 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 and Oritavancin has not been evaluated..
The performance of Delafloxacin was determined using the OptiRead and the digital reading device (VIZION) (*Streptococcus* spp.) and the VIZION (*H. influenzae*) reading methods only. The use of an alternative reading method when testing Delafloxacin has not been evaluated.

The ability of Sensititre to detect non-susceptibility of *S. pneumoniae* to delafloxacin has not been established due to an insufficient number of non-susceptible isolates encountered at the time of comparative testing and the occurrence of potential very major errors (ARIS/OptiRead, 50% very major error rate adjusted to 0%; digital reading device (VIZION) very major error rate of 100% adjusted to 50%). If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for *S. pneumoniae* and delafloxacin.

Due to a lack of interpretive criteria other than susceptible, isolates of *S. pneumoniae* and *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 VISION, ARIS/OptiRead

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* pp. 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).

C Instrument Description Information:

1. Instrument Name:
   Not Applicable

2. Specimen Identification:
   Not Applicable

3. Specimen Sampling and Handling:
   Not Applicable

4. Calibration:
   Not Applicable

5. Quality Control:
   Not Applicable

V Substantial Equivalence Information:

A Predicate Device Name(s):
The Sensititre 20-24-hour Haemophilus influenzae/Streptococcus pneumoniae MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.00025-8µg/mL

B Predicate 510(k) Number(s):
K172274

C Comparison with Predicate(s):

Device & Predicate Device(s):	**K223844 Delafloxacin**	**K172274 Delafloxacin**
Device Trade Name	Sensititre *Haemophilus/ Streptococcus pneumoniae* (HP) MIC Susceptibility Plates with Delafloxacin	Same
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 fastidious isolates	Same
Test Panel	96 well plate is dosed with selected antimicrobial agents	Same

	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, non-CO_2	same
General Device Characteristic Differences		
Test Organisms	*S. pyogenes, S. agalactiae, S. anginosus grp, S. pneumoniae* and *H. influenzae*	*S. pyogenes, S. agalactiae, S. anginosus grp,*
Antibiotic/Organism and Dilution Range	Delafloxacin for *S. pneumoniae* and *Streptococcus* spp. 0.00025 – 8 µg/mL Delafloxacin for *H. influenzae* 0.000125 – 8 µg/mL	Delafloxacin for *Streptococcus* spp. 0.00025 – 8 µg/mL
Read Method	*Streptococcus* spp. and *S. pneumoniae* – digital reading device (VIZION), Sensititre ARIS/OptiRead *H. influenzae* – digital reading device (VIZION)	*Streptococcus* spp. – digital reading device (VIZION), Sensititre ARIS/OptiRead

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 M100-S027: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh Informational Supplement

CLSI M7-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth 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* and 23 isolates of *Streptococcus* spp. (including six isolates of *S. pneumoniae*) for a total of 360 data points for *H. influenzae* read using the digital viewing device (VIZION) and 828 data points each for the digital viewing device (VIZION) and ARIS/OptiRead for *Streptococcus* spp. 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). Reproducibility was greater than 95% for both the digital viewing device (VIZION) and ARIS/OptiRead read methods for *Streptococcus* spp. including *S. pneumoniae*. Results were considered to be acceptable.

2. Linearity:
   Not Applicable

3. Analytical Specificity/Interference:
   Not Applicable

4. Assay Reportable Range:
   No Applicable

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

Quality control strains recommended by the CLSI were tested with delafloxacin at four sites and included *H. influenzae* ATCC 49247 and *S. pneumoniae* ATCC 49619. The QC strains were tested a minimum of 20 times per site and read using the digital reading device (VIZION) only for *H. influenzae* and digital reading device (VIZION) and ARIS/OptiRead for *S. pneumoniae*. QC strains were also tested with the reference method. The results demonstrate that the Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC Susceptibility plates with delafloxacin produced quality control results in the recommended range >95% of time (Table 1).

Table 1. QC Results for *H. influenzae* and *S. pneumoniae* with Delafloxacin with the Reference Method, the Digital Reading Device (Vizion) and ARIS/OptiRead

QC Organism	Delafloxacin Expected Range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre Digital Reading Device (VIZION)	Sensititre ARIS/OptiRead
H. influenzae ATCC 49247	0.00025 – 0.001 µg/mL	0.000125	-	-	NA
		0.00025	-	7	NA
		0.0005	81	73	NA
		0.001	1	2	NA
		0.002	-	-	NA
		0.004	-	-	NA
		0.008	-	-	NA
		0.015	-	-	NA
		0.03	-	-	NA
		0.06	-	-	NA
		0.12	-	-	NA
		0.25	-	-	NA
		0.5	-	-	NA
		1	-	-	NA
		2	-	-	NA
		4	-	-	NA
		8	-	-	NA

S. pneumoniae ATCC 49619	0.004 – 0.015 µg/mL	0.00025	-	-	-
		0.0005	-	-	-
		0.001	-	-	-
		0.002	-	-	-
		0.004	29	-	89
		0.008	58	83	1
		0.015	-	7	-
		0.03	-	-	-
		0.06	-	-	-
		0.12	-	-	-
		0.25	-	-	-
		0.5	-	-	-
		1	-	-	-
		2	-	-	-
		4	-	-	-
		8	-	-	-

Inoculum Density: Inoculum density checks were performed for all QC, reproducibility and challenge isolates and 10% of clinical isolates tested. For sites 1 and 2, colony counts were approximately 1 log higher than expected for QC (Sensititre and reference), clinical isolates (Sensititre) and reproducibility (Sensititre) for *H. influenzae* and QC isolates for *S. pneumoniae.* Because all quality control results were in the expected range, the colony count data is considered to be acceptable.

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 *S. pneumoniae* or *H. influenzae.*

6. Detection Limit:
   Not Applicable

7. Assay Cut-Off:
   Not Applicable

8. Accuracy (Instrument):
   Not Applicable

9. Carry-Over:
   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of the Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* MIC Susceptibility plates with delafloxacin 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* and both digital reading device (VIZION) and OptiRead for *S. pneumoniae.* 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 delafloxacin inoculation method limitation in the device labeling to include *S. pneumoniae* and *H. influenzae* (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*** *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*** *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 modified the existing delafloxacin read method limitation in the device labeling to include *S. pneumoniae* and *H. influenzae* (modifications in bold font):

> *The performance of delafloxacin* ***was determined using the OptiRead and digital reading device (VIZION) (Streptococcus spp.) and the VIZION (H. influenzae)*** *reading methods only. The use of an alternative reading method when testing delafloxacin has not been evaluated.*

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

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

The testing conditions for the Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC Susceptibility plates with delafloxacin consisted of the following:

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 and adjusted to approximate a 0.5 McFarland standard. After mixing, 100 µL of the *Streptococcus* suspension was inoculated into 11 mL of CAMHBT+LHB (CP-114). Susceptibility panels were inoculated with 100 µL of the organism suspension using the Sensititre AIM.
- 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.

For *Streptococcus* species, the device labeling indicates that cation-adjusted Mueller Hinton broth with TES buffer and lysed horse blood (CAMHBT+LHB, CP-112) should be utilized for inoculating plates read manually (using the digital reading device VIZION or the Sensititre manual reader) and cation-adjusted Mueller Hinton broth with TES buffer and lysed horse blood (CAMHBT+LHB, CP-114) should be utilized for inoculating plates read automatically.

For the purpose of the comparative study, only CAMHBT+LHB, CP-114 was utilized. To address the use of only CAMHBT+LHB (product CP-114) for panels intended to be read by both the digital reading device (VIZION) and ARIS/OptiRead, the sponsor included the following limitation in the device labeling:

> *AST testing of delafloxacin with S. pneumoniae and read using the digital reading device (VIZION) and ARIS/OptiRead was performed using cation-adjusted Mueller Hinton broth with TES buffer and lysed horse blood (CAMHBT+LHB, CP-114)*

H. influenzae. 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 99.1% and 99.3% for EA and CA, respectively. There were no major or minor errors but there were three potential very major errors for a very major error rate of 15.8%. All three potential very major errors were within ± one dilution of the reference method. An additional 16 resistant strains were accurately detected as resistant. Due to the lack of any interpretive criteria other than susceptible for delafloxacin with *H. influenzae*, further analysis of the errors was performed, and adjustments were made by considering the MIC values where the errors occurred. All potential very major errors had an MIC value that was one doubling dilution from the reference result and thus in essential agreement (EA) with the reference method resulting in an adjusted very major error rate of 0% which is acceptable (Table 2). The adjusted very major error rate is addressed in the following footnote to the performance characteristics table in the device labeling:

> *Three of 19 non-susceptible isolates of H. influenzae gave potential very major errors (15.8%). Due to the lack of an intermediate or resistant interpretive category, the adjusted very major error rate is 0%.*

S. pneumoniae. A total of 199 clinical isolates and 50 challenge (total 249 isolates) of *S. pneumoniae* were evaluated. For *S. pneumoniae* MICs interpreted using the digital reading device (VIZION), the combined clinical and challenge results were acceptable at 99.8% and 99.2% for EA and CA, respectively. There were no major or minor errors but there were two potential very major errors for a very major error rate of 100% (Table 3). One of these potential very major errors was associated with MIC value that was within ± one dilution of the reference method. Due to the lack of an intermediate or resistant interpretive category our analysis takes into consideration MIC results that are within essential agreement with the reference method and the error rate is adjusted accordingly. The adjusted very major error rate for *S. pneumoniae* using the digital reading device (VIZION) is 50%. The high very major error rate is addressed in the labeling limitation (see below).

For *S. pneumoniae* read using ARIS/OptiRead, the combined clinical and challenge results were acceptable at 99.2% and 99.6% for EA and CA, respectively. There were no major or minor errors but there was one potential very major error for a very major error rate of 50% (Table 4). The result providing the potential very major error was associated with MIC values that were within ± one dilution of the reference method. Due to the lack of an intermediate or resistant interpretive category our analysis takes into consideration MIC results that are within essential agreement with the reference method and the error rate is adjusted accordingly. The adjusted very major error rate for *S. pneumoniae* using ARIS/OptiRead is 0%. The very major error rate is addressed in the labeling limitation (see below).

Because only two non-susceptible isolates of *S. pneumoniae* were evaluated and because of the occurrence of very major errors, the following limitation was included in the device labeling:

> *The ability of Sensititre to detect non-susceptibility of S. pneumoniae to delafloxacin has not been established due to an insufficient number of non-susceptible isolates encountered at the time of comparative testing and the occurrence of potential very major errors (ARIS/OptiRead, 50% very major error rate adjusted to 0%; digital reading device (VIZION) very major error rate of 100% adjusted to 50%). If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for S. pneumoniae and delafloxacin.*

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 *S. pneumoniae* and *H. influenzae* other than "susceptible" and states that isolates yielding an MIC result other than susceptible should be submitted to a reference laboratory for further testing. 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, isolates of S. pneumoniae and H. influenzae yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.*

Table 2. Delafloxacin 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[a]	No. S	min	maj	vmj
***H. influenza* (Susceptible ≤ 0.004 µg/mL) for isolates from CABP**													
Clinical	393	389	99.0	388	384	99.0	391	99.5	17	376	0	0	2
Challenge	50	50	100	50	50	100	49	98.0	2	48	0	0	1
Total	443	439	99.1	438	434	99.1	440	99.3	19	424	0	0	3[b]

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible".

[b] Very major error rate 15.8% adjusted to 0%

Table 3: Delafloxacin results for *S. pneumoniae* 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
***S. pneumoniae* (Susceptible ≤0.03 µg/mL) for isolates from CABP**													
Clinical	199	196	98.5	199	196	98.5	198	99.5	1	198	0	0	1
Challenge	50	50	100	50	50	100	49	98.0	1	49	0	0	1
Total	249	246	98.8	249	246	98.8	247	99.2	2	247	0	0	2[b]

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible".

[b] Very major error rate 100% adjusted to 50%; addressed in limitation

Table 4: Delafloxacin results for *S. pneumoniae* with ARIS/OptiRead

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS[a]	No. S	min	maj	vmj
***S. pneumoniae* (Susceptible ≤0.03 µg/mL) for isolates from CABP**													
Clinical	199	197	99.0	199	197	99.0	199	100	1	198	0	0	0
Challenge	50	50	100	50	50	100	49	98.0	1	49	0	0	1
Total	249	247	99.2	249	247	99.2	248	99.6	2	247	0	0	1[b]

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible".

[b] Very major error rate 50% adjusted to 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. 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 appropriate read method for each species evaluated. 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 delafloxacin using the digital reading device (VIZION) indicate a trend toward lower MICs compared to the reference method. Evaluation of results for *S. pneumoniae* and delafloxacin read using the digital reading device (VIZION) indicate a trend toward higher MICs compared to the reference method. No trending was observed for *S. pneumoniae* read using ARIS/OptiRead (Table 5). To address trending the sponsor added the following footnote to the performance table:

> *Delafloxacin MIC values tended to be in exact agreement or at least one dilution higher when testing S. pneumoniae with the digital reading device (VISION) and at least one dilution lower when testing H. influenzae with VIZION compared to the CLSI reference broth microdilution method.*

Table 5. Trending Observed by Read Method for *H. influenzae* and *S. pneumoniae* with Delafloxacin

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	442	195 (44.1)	231 (52.3)	16 (3.6)	-40% (-40% to -35%)	Yes Low
S. pneumoniae /digital reading device (VIZION) read	249	10 (4.0)	142 (57.0)	97 (39.0)	35% (28% to 41%)	Yes High
S. pneumoniae/ ARIS/OptiRead	249	19 (7.6)	169 (67.9)	61 (24.5)	17% (11% to 23%)	No

Testing/Reporting MICs for Non-indicated Species. For this review, the interpretative 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:

> *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-Identified Interpretive Criteria for Delafloxacin, Community Acquired Bacterial Pneumonia (CABP)

Organism	Interpretive Criteria for Delafloxacin[a]		
	Susceptible	Intermediate[b]	Resistant[b]
H. influenzae	≤ 0.004	-	-
S. pneumoniae	≤ 0.03	-	-

[a] FDA STIC Webpage
[b] The current absence of resistant isolates precludes defining any results other than "Susceptible".

F Other Supportive Instrument Performance Characteristics Data:
Not Applicable

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 Delafloxacin when revised breakpoints for delafloxacin 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 delafloxacin 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.