510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K172274

B. Purpose for Submission:

To obtain a substantial equivalence for the addition of Delafloxacin at concentrations 0.00025-8 µg/mL to the Sensititre 20-24 MIC for susceptibility testing of fastidious Gram positive organisms.

C. Measurand:

Delafloxacin 0.00025-8 µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST) growth based detection

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

The Sensititre 20-24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.00025-8 µg/mL

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code:

   JWY – Manual Antimicrobial Susceptibility Test Systems

LRG – Instrument for Auto Reader and Instrumentation of Overnight Susceptibility Systems

LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended use(s):

   The 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.

2. Indication(s) for use:

   The Sensititre 20-24 hours *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 Delafloxacin in the dilution range of 0.00025 - 8 µg/mL for testing fastidious *Streptococcus* spp. on the Sensititre 20-24 hour *Haemophilus influenzae*/*Streptococcus pneumoniae* MIC panel or Breakpoint Susceptibility System.

   The approved primary "Indications for Use" and clinical significance for fastidious *Streptococcus* spp. isolates:

   Streptococcus pyogenes
   Streptococcus agalactiae
   Streptococcus anginosus group

3. Special conditions for use statement(s):

   For prescription use only

   The following information is included in 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 isolates were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory (table in Instructions for Use includes *S. pyogenes*, *S. agalactiae* or *S. anginosus* for Delafloxacin).

- Studies were performed using the AIM autoinoculator. Performance with other inoculation methods was not determined.

- Resistance mechanism characterization was not provided for all organisms at the time of comparative testing, and therefore the performance of the Sensititre Delafloxacin for fastidious gram positive organisms is unknown for isolates with the following resistance mechanisms: topoisomerase IV and DNA gyrase Quinolone-Resistant Determining Regions (QRDRs), or altered efflux.

- The performance of Delafloxacin with gram positive organisms was performed using the AutoReader (OptiRead) and VIZION reading methods only. The use of an alternative reading method when testing delafloxacin has not been evaluated.

- Two *S. anginosus* isolates were determined as non-susceptible by the reference method. Although both results were within Essential Agreement, one very major discrepancy was observed when compared to the reference method. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for Delafloxacin with organism *S. anginosus* when the Senstitre MIC is 0.06 µg/mL.

4. Special instrument requirements:

   Sensititre AIM for device inoculation
   Sensititre VIZION or OptiRead for plate reading

I. Device Description:

Sensititre MIC Susceptibility plate MIC panels are multiwell plastic microtiter plates, dosed with dried, stabilized antimicrobials. 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.

Antimicrobial susceptibility test results can be determined by manually reading of growth using the digital viewing device (VIZION) or automatically on an autoreader (OptiRead) using fluorescence.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Sensititre *Haemophilus influenzae*/*Streptococcus pneumoniae* MIC Susceptibility Plate, Clindamycin

2. Predicate 510(k) number(s):

   K140985

3. Comparison with predicate:

Table 1. Comparison with Predicate Device

Similarities		
Item	Sensititre *Haemophilus*/*Streptococcus pneumoniae* MIC Susceptibility plates, Delafloxacin (K172274)	Predicate: Sensititre *Haemophilus*/*Streptococcus pneumoniae* MIC Susceptibility plates, Clindamycin (K140985)
Intended Use	The 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 dosed with selected antimicrobial agents then dried	Same
Test Organism	*Streptococcus* sp.	Same
Results	Report results as Minimum Inhibitory Concentration (MIC) and interpretive criteria (S, I, R)	Same
Reading Method	Results can be read by the following methods: 1) Automatically - with the OptiRead (fluorogenic substrate technology) 2) On the VIZION - Digital Viewing Device	Same
Panel Inoculation	Automated inoculation using AIM	Same
Incubation	20-24 hours	Same

Differences		
Item	Sensititre *Haemophilus*/*Streptococcus pneumoniae* MIC Susceptibility plates, Delafloxacin (K172274)	Predicate: Sensititre *Haemophilus*/*Streptococcus pneumoniae* MIC Susceptibility plates, Clindamycin (K140985)
Antimicrobial	Delafloxacin	Clindamycin

K. Standard/Guidance Document Referenced (if applicable):

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

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

3. CLSI M7-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition

L. Test Principle:

The Sensititre *Haemophilus influenzae*/*Streptococcus pneumoniae* (HP) MIC Susceptibility plates are multi-well plastic microtitre plates that contain doubled dilution of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read by the VIZION or by use of an automated reader (OptiRead).

The 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.

M. Performance Characteristics:

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*

      A reproducibility study was performed at four sites using 10 *Streptococcus* isolates. The isolates were tested in triplicate over three different days for each reading method (VIZION, OptiRead). The isolates tested in the reproducibility study included one isolate each of *S. pyogenes*, *S. dysgalactiae*, *S. mitis*, and *S. sanguinis* and two isolates each of *S. agalactiae*, *S. oralis*, and *S. anginosus*. The Sensititre AIM was used for plate inoculation. The mode MIC value was pre-determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC

value. There were no "off-scale" results for either reading method. Reproducibility was calculated and was reported as greater than 95% for both the VIZION and the OptiRead methods. The results were acceptable.

b. *Linearity/assay reportable range:*

Not Applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Quality Control Testing*:*

The QC isolate recommended by both FDA and CLSI, namely *S. pneumoniae* ATCC 49619 was tested a sufficient number of times (i.e., at least 20/site) at each testing site. The results are summarized in Table 2 below. The quality control results are acceptable.

Table 2. Quality Control Results – Delafloxacin

Organism	Conc. (µg/mL)	Reference Panel	OptiRead	VIZION
S. pneumoniae ATCC 49619 Expected Result: 0.004-0.015 µg/mL	0.002	0	0	0
	0.004	29	0	0
	0.008	58	89	83
	0.015	0	1	7
	0.03	0	0	0

Inoculum Density Check:

The inoculum density of each quality control, reproducibility, clinical and challenge isolate was determined each day of testing. The inoculum was prepared to achieve turbidity equivalent to a 0.5 McFarland standard. A total of 407 inoculum density checks were performed for each test and reference panel for quality control, clinical and challenge isolates and sufficient number of checks were performed on the test panel for the reproducibility study. The colony counts obtained for all isolates were within acceptable range.

d. *Detection limit:*

Not Applicable

e. *Analytical specificity:*

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

The panel was prepared according to the CLSI recommendation and used as the reference method. During the course of the clinical trial, all Sensititre dried MIC panels were inoculated using the Sensititre Autoinoculator (AIM) and the same panel was read on both the VIZION and the OptiRead in a blinded manner.

Clinical:

Clinical testing was conducted at four sites using a total of 258 fresh clinical *Streptococcus* isolates that included *S. pyogenes* (100), *S. agalactiae* (106) and *S. anginosus* group (52).

Challenge:

Additional stock challenge isolates were tested at one study site. Challenge testing was conducted using 59 stock *Streptococcus* isolates that included 23 *S. pyogenes*, 23 *S. agalactiae* and 13 *S. anginosus* isolates.

In total, 317 combined (Clinical and Challenge) isolates were evaluated. Tables 3 and 4 below illustrate the performance for the VIZION and the OptiRead, respectively.

The growth rate for each plate read in the clinical and challenge studies was 100%.

Table 3. Combined (Clinical and Challenge) Performance Summary of Gram Positive Organisms – Read by VIZION

Delafloxacin	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	NS	min	maj	vmj
S. pyogenes	123	123	100	123	123	100	123	100	N/A	1	N/A	0	0
S. agalactiae	129	129	100	129	129	100	129	100	3	N/A	0	0	0
S. anginosus group	65	64	98.5	65	64	98.5	65	100	N/A	2	N/A	0	0
All Organisms*	317	316	99.7	317	316	99.7	317	100	3	3	0	0	0

Table 4. Combined (Clinical and Challenge) Performance Summary of Gram Positive Organisms – Read by OptiRead

Delafloxacin	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	NS	min	maj	vmj
S. pyogenes	123	122	99.2	123	122	99.2	122	99.2	N/A	1	N/A	1	0
S. agalactiae	129	128	99.2	129	128	99.2	128	99.2	3	N/A	1	0	0
S. anginosus group	65	64	98.5	65	64	98.5	64	98.5	N/A	2*	N/A	0	1*
All Organisms	317	314	99.1	317	314	99.1	314	99.1	3	3	1	1	1

* Of the two non-susceptible isolates, the MIC value of the isolate that gave a very major error (50% very major error rate) was within essential agreement of the reference MIC value; therefore the adjusted very major error rate is 0%.

EA - Essential Agreement
CA - Category Agreement
R- resistant isolates
NS – non-susceptible
maj – major discrepancies
vmj- very major discrepancies
min – minor discrepancies

Evaluable results are those that are on-scale for both the reference panel and the Sensititre panel. Essential agreement (EA) occurs when there is agreement between the MIC result of the reference method and that of Sensititre panel within plus or minus one serial two-fold dilution of the antibiotic. Category agreement occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel result.

As shown in Tables 3 and 4, the percent CA and EA values were above 90%, and are therefore, acceptable as described in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 2009*. A comparative evaluation of performance data of the VIZION and OptiRead methods revealed very little difference.

In addition, there was one very major error (50% very major error rate) observed for one *S. anginosus* isolate read by the OptiRead; however, because there is no intermediate breakpoint for *S. anginosis* and because the result fell within essential agreement of the reference method, the error rate was determined to be acceptable. Taking this into consideration, the adjusted very major error rate is 0%. Furthermore, given that there were only two non-susceptible isolates tested, the following footnote is included in the labeling:

> *Two S. anginosus isolates were determined as non-susceptible by the reference method. Although both results were within Essential Agreement, one very major discrepancy was observed when compared to the reference method. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for Delafloxacin with organism S. anginosus when the Senstitre MIC is 0.06 µg/mL.*

MIC Trends:

Table 5. Summary of Evaluation of MIC Trends (Combined clinical and challenge data)

Delafloxacin	Total	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
	S. pyogenes					
VIZION[a]	123	0	12	79	32	0
		(9.76%)		(64.23%)	(26.02%)	
OptiRead[b]	123	0	5	60	57	1
		(4.07%)		(48.78%)	(47.15%)	
	S. agalactiae					
OptiRead[c]	129	1	42	67	19	0
		(33.33%)		(51.94%)	(14.73%)	

[a]Difference between the higher and lower dilutions for VIZION/*S. pyogenes* is: 16.26%; 95% C.I. (6.73% to 25.60%)
[b]Difference between the higher and lower dilutions for OptiRead/*S. pyogenes* is: 43.09%; 95% C.I. (33.09% to 52.16 %)
[c]Difference between the higher and lower dilutions for OptiRead/*S. agalactiae* is: -18.60%; 95% C.I. (-28.52% to -8.22 %)
Note: A positive percent difference value indicates higher MIC when compared to the reference method;
A negative percent difference value indicates lower MIC when compared to the reference method.

As illustrated in Table 5, there was a difference in results trending either above or below the reference method. The data for *S. pyogenes* demonstrates a trend for one doubling dilution higher for results read by the VIZION and OptiRead compared to the reference method. As a result, the following footnote was included in the performance section of the package insert:

> *Delafloxacin MIC values for S. pyogenes tended to be one doubling dilution higher with the VIZION and OptiRead as compared to the reference microdilution method.*

In addition, data demonstrated a trend of one doubling dilution lower compared to the reference method for results read by the OptiRead for *S. agalactiae*. As a result, the following footnote was included in the performance section of the package insert:

> *Delafloxacin MIC values for S. agalactiae tended to be one doubling dilution lower with the OptiRead as compared to the reference microdilution method. If critical to patient care, S. agalactiae isolates with an MIC result of 0.06 µg/mL should be retested with an alternative method or sent to a reference lab.*

There were no trends noted for *S. anginosus*.

b. Matrix comparison:

N/A

3. Clinical studies:

a. Clinical Sensitivity:

N/A

b. Clinical specificity:

N/A

c. Other clinical supportive data (when a. and b. are not applicable):

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Delafloxacin are as listed in Table 6.

Table 6. Interpretive Criteria for Delafloxacin (µg/mL)

	Susceptible (S)	Intermediate (I)	Resistant (R)
S. pyogenes	≤0.06	*	*
S. agalactiae	≤0.06	0.12	≥0.25
S. anginosus Group	≤0.06	*	*

**Only susceptible interpretative criteria are defined for these two organisms*.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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