510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K172454

B. Purpose for Submission:

To obtain a substantial equivalence for the addition of Delafloxacin at concentrations 0.004-8 µg/mL to the Sensititre 18-24 MIC for susceptibility testing of non-fastidious Gram negative organisms.

C. Measurand:

Delafloxacin 0.004-8 µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST) growth based detection

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.004-8 ug/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 MIC and Breakpoint Susceptibility system is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious Gram negative isolates, comprising of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and other non-*Enterobacteriaceae* and of non-fastidious Gram positive isolates, comprising of *Staphylococcus spp*., *Enterococcus spp.*, and Beta haemolytic *Streptococci* other than *S. pneumoniae*.

2. Indication(s) for use:

   The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious isolates.

   This 510(k) is for Delafloxacin in the dilution range of 0.004 - 8 µg/mL for testing non-fastidious Gram negative organisms on the Sensititre 18-24 hour MIC panel.

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

   Escherichia coli
   Klebsiella pneumoniae
   Enterobacter cloacae
   Pseudomonas aeruginosa

3. Special conditions for use statement(s):

   For prescription use only

   The following information is included in labeling:

   - Studies of Delafloxacin with *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa* were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Delafloxacin has not been evaluated.

   - Resistance mechanism characterization was not provided for all organisms at the time comparative testing, and therefore the performance of the Sensititre Delafloxacin for non-fastidious gram negative 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 negative 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.

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 multi-well plastic micro-titer plates, dosed with dried, stabilized antimicrobials. It is a miniaturized version of the classic broth dilution methods and can provide both qualitative and quantitative susceptibility results. After inoculation, plates are sealed with an adhesive seal, incubated at 34-36°C for 18-24 hours and examined for bacterial growth.

Antimicrobial susceptibility test results can be determined by 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 18-24 hour Susceptibility MIC Plates, Ceftaroline

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

K111615

3. Comparison with predicate:

Table 1. Comparison with Predicate Device

Similarities		
Item	Sensititre 18-24 Susceptibility, Delafloxacin (K172454)	Predicate: Sensititre 18-24 Susceptibility, Ceftaroline (K111615)
Intended Use	The Sensititre MIC and Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious Gram negative isolates, comprising of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and other non-*Enterobacteriaceae* and of non-fastidious Gram positive isolates, comprising of *Staphylococcus spp*., *Enterococcus spp*., and Beta haemolytic *Streptococci* other than *S. pneumoniae*	The Sensititre HP MIC Susceptibility plate with Ceftaroline (0.015-32 ug/ml) and the Sensititire 18-24 hour MIC Susceptibility system Test panel with Ceftaroline (0.015-64ug/ml) are intended for use with the Sensititre MIC or BP Susceptibility System.
Test Panel	96-well plate dosed with selected antimicrobial agents then dried	Same
Results	Report results as Minimum Inhibitory Concentration (MIC) and interpretive criteria (S, I, R)	Same
Read Method	Automated and Manual	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
Test Organism	Non-fastidious Gram negative isolates	Same
Incubation	18-24 hours	Same

Differences		
Item	Sensititre 18-24 Susceptibility, Delafloxacin (K172454)	Predicate: Sensititre 18-24 Susceptibility, Ceftaroline (K111615)
Drug	Delafloxacin (0.004-8 µg/mL)	Ceftaroline (0.015-32 µg/ml)

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 18-24 hour MIC or Breakpoint Susceptibility System 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 18 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 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 substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The 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 11 Gram negative organisms that included five *E. coli* isolates, four *K. pneumoniae* isolates, one *E. cloacae* isolate, and one *P. aeruginosa* isolate. The isolates were tested in triplicate over three different days for each reading method (i.e., VIZION and OptiRead). 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. All MIC results were on-scale by both reading methods. Reproducibility was 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 isolates recommended by both FDA and CLSI, namely *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were 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
E. coli ATCC 25922 Expected Result: 0.008-0.03 µg/mL	0.004	0	0	0
	0.008	6	26	9
	0.015	73	54	71
	0.03	1	0	0
	0.06	0	0	0
P. aeruginosa ATCC 27853 Expected Result: 0.12-0.5 µg/mL	0.06	0	0	0
	0.12	47	69	74
	0.25	33	11	6
	0.5	0	0	0
	1	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 235 inoculum density checks for each test and reference panel for quality control and challenge isolates, 294 for the clinical study reference test, 304 for the clinical study test device,and 129 checks for the reproducibility study were performed. 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 reference panel used for the comparison 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 264 fresh clinical *Enterobacteriaceae* isolates that included *E. coli* (111), *K. pneumoniae* (107), and *E. cloacae* (46). In addition, 40 *P. aeruginosa* fresh isolates were tested.

Challenge:

Additional 75 stock challenge isolates were tested at one study site. Challenge testing was conducted using *E. coli* (16), *K. pneumoniae* (28), *E. cloacae* (11), and *P. aeruginosa* (20) isolates.

In total, 379 combined (Clinical and Challenge) isolates were evaluated. Tables 3 and 4 below illustrate the performance for the OptiRead and the VIZION, 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 Negative Organisms – Read by OptiRead*

Delafloxacin	Total	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min	maj	vmj
Enterobacteraceae	319	312	97.8	282	275	97.5	309	96.9	166	10	0	0
*P. aeruginosa***	59	59	100	49	49	100	55	93.2	22	4	0	0
All Organisms	378	371	98.1	331	324	97.9	364	96.3	188	14	0	0

*See legend for abbreviations under Table 4.

**One *P. aeruginosa* isolate did not produce a signal on the OptiRead and therefore, excluded from the performance analysis.

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

Delafloxacin	Total	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min	maj	vmj
Enterobacteraceae	319	315	98.7	282	278	98.7	311	97.5	166	8	0	0
P. aeruginosa	60	60	100	51	51	100	55	91.7	22	5	0	0
All Organisms	379	375	98.9	333	329	98.8	366	96.6	188	13	1	1

EA - Essential Agreement
CA - Category Agreement
R- resistant isolates
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 for the OptiRead and VIZION methods revealed very little difference.

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**
	All *Enterobacteriaceae*					
OptiRead[a]	288	7	102	143	36	0
		(37.85%)		(49.65%)	(12.50%)	
VIZION[b]	290	4	80	169	37	0
		(28.97%)		(58.28%)	(12.76%)	

[a]Difference between the higher and lower dilutions for OptiRead/*Enterobacteriaceae* is: -25.35%; 95% C.I. (-31.97% to -18.43%)
[b]Difference between the higher and lower dilutions for VIZION/*Enterobacteriaceae* is: -16.21%; 95% C.I. (-22.62% to -9.65%)

The total number of isolates in Table 5 reflects *Enterobacteriaceae* isolates with on-scale MIC values and in which a determination could be made of higher or lower values compared to the reference method. As illustrated in Table 5, there was a difference in results trending below the reference method. The data for all *Enterobacteriaceae* demonstrated a trend for one doubling dilution lower 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 Enterobacteriaceae tended to be one doubling dilution lower with the OptiRead and when manually read by the VIZION as compared to the reference microdilution method.*

There were no trends noted for *P. aeruginosa*.

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)
*Enterobacteriaceae**	≤0.25	0.5	≥1
P. aeruginosa	≤0.5	1	≥2

**E. coli, K. pneumoniae, and E. cloacae only.*

N. Proposed Labeling:

The labeling is sufficient and 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.