510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K171870

B. Purpose for Submission:

To obtain a substantial equivalence for the addition of Delafloxacin at concentrations 0.0005-8 µg/mL to the Sensititre 18-24 MIC for susceptibility testing of non-fastidious Gram positive organisms.

C. Measurand:

Delafloxacin 0.0005-8 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 18-24 hour MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.0005 – 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 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 hours MIC or Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing for non-fastidious isolates.

   This 510(k) is for Delafloxacin in the dilution range of 0.0005 - 8 µg/mL for testing non-fastidious gram positive organisms on the Sensititre 18-24 hour MIC panel.

   The approved primary "Indications for Use" and clinical significance for non-fastidious Gram positive isolates:

   Staphylococcus aureus (including MRSA and MSSA)
   Staphylococcus haemolyticus
   Staphylococcus lugdunensis
   Enterococcus faecalis

3. Special conditions for use statement(s):

   For prescription use only

   The following information is included in labeling

   - Studies of Delafloxacin with *Staphylococcus aureus* (MRSA and MSSA), *Enterococcus faecalis*, and Coagulase Negative *Staphylococcus* spp. (*Staphylococcus haemolyticus* and *Staphylococcus lugdunensis*) were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Delafloxacin has not been evaluated.

- The ability of the Sensititre system to detect isolates of *S. haemolyticus* that are non-susceptible to Delafloxacin is unknown because an insufficient number of isolates was available at the time of the comparative testing. If critical to patient care, *S. haemolyticus* that are determined to be non-susceptible Sensititre results should be tested with an alternative method or sent to a reference lab.

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

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 micro-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):

   MicroScan Dried Gram-Negative and Gram-Positive MIC/Combo Panels

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

   K010159

3. Comparison with predicate:

Table 1. Comparison with Predicate Device

Similarities		
Item	Sensititre 18-24 Susceptibility, Delafloxacin (K171870)	Predicate: Microscan Dried Gram-Negative and Gram-Positive MIC/Combo Panels, Gatifloxacin (K010159)
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*	MicroScan Dried Gram-Negative and Gram-Positive MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative Gram-Negative bacilli and Gram-Positive cocci
Test Panel	96-well plate dosed with selected antimicrobial agents then dried	Same
Test Organism	Non-fastidious gram positive isolates	Same
Results	Report results as Minimum Inhibitory Concentration (MIC) and interpretive criteria (S, I, R)	Same
Read Method	Automated and Manual	Same

Differences		
Item	Sensititre 18-24 Susceptibility, Delafloxacin (K171870)	Predicate: Microscan Dried Gram-Negative and Gram-Positive MIC/Combo Panels, Gatifloxacin (K010159)
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	Organism growth/turbidity based reading and interpretation via manual read or MicroScan instrumentation (Walkaway, AutoScan-4)
Antimicrobial	Delafloxacin	Gatifloxacin
Incubation	18-24 hours	16-20 hours

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 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. Analytical performance:

   a. *Precision/Reproducibility:*

      A reproducibility study was performed at four sites using 13 isolates of non-fastidious gram positive organism. The isolates were tested in triplicate over three different days for each reading method (VIZION, OptiRead). The isolates tested in the reproducibility study included *S. aureus* (five MRSA and five MSSA isolates), *S. haemolyticus* (one isolate), and *E. faecalis* (one VRE and one VSE isolate). 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 was a single "off-scale" result for each study. Reproducibility was calculated for both "best case" and "worst case" scenarios for each reading method. 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 *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 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
S. aureus ATCC 29213 Expected Result: 0.001-0.008 µg/mL	0.0005	0	0	0
	0.001	4	0	0
	0.002	72	71	85
	0.004	6	16	2
	0.008	0	0	0
	0.015	0	0	0
E. faecalis ATCC 29212 Expected Result: 0.015-0.12 µg/mL	0.008	0	0	0
	0.015	0	0	0
	0.03	54	41	46
	0.06	28	46	41
	0.12	0	0	0
	0.25	0	0	0

Inoculum Density Check:

The inoculum density of the quality control organisms tested was determined each day of testing. The inoculum was prepared to achieve turbidity equivalent to a 0.5 McFarland standard. A total of 338 inoculum density checks were performed. The colony counts obtained for quality control, reproducibility and clinical 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).

Clinical:

Clinical testing was conducted at four sites using 440 Gram positive organisms that included *Staphylococcus spp*. (200 MSSA, 200 MRSA, 20 *S. haemolyticus*, and 20 *S. lugdunensis*) and 60 *E. faecalis* isolates for a cumulative of 500 fresh clinical isolates.

Challenge:

Additional stock challenge isolates were tested at one study site. Challenge testing was conducted using 110 Gram positive organisms that included 48 MSSA, 52 MRSA, three *S. haemolyticus*, two *S. lugdunensis* and five isolates of *E. faecalis*.

In total, 610 combined (Clinical and Challenge) isolates were evaluated. Tables 3 and 4 below illustrate the performance for the VIZION and the OptiRead, respectively.

The growth rates for the VIZION and OptiRead methods were 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	min (%)	maj (%)	vmj (%)
S. aureus (MSSA)	248	247	99.6	244	244	100	244	98.4	1	4	0	0
S. aureus (MRSA)	252	252	100	252	252	100	232	92.1	42	20	0	0
E. faecalis	65	65	100	65	65	100	65	100	21	0	0	0
S. haemolyticus	23	23	100	23	23	100	23	100	0	0	0	0
S. lugdunensis	22	22	100	22	22	100	N/A	N/A	N/A	N/A	N/A	N/A
All Organisms*	610	609	99.8	606	606	100	564	95.9	64	24	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	min (%)	maj (%)	vmj (%)
S. aureus (MSSA)	248	237	95.6	244	236	96.7	242	97.6	1	6	0	0
S. aureus (MRSA)	252	248	98.4	252	248	98.4	237	94	43	14	0	0
E. faecalis	65	64	98.5	65	64	98.5	63	96.9	21	2	0	0
S. haemolyticus	23	22	95.7	23	22	95.7	22	95.7	0	1	0	0
S. lugdunensis	22	22	100	22	22	100	N/A	N/A	N/A	N/A	N/A	N/A
All Organisms*	610	593	97.2	606	592	97.7	564	95.9*	65	23	0	0

*Note: The performance for EA includes all organisms tested; however, due to lack of interpretive criteria for *S. lugdunensis*, those isolates were not included in analysis of CA. The 95.9% CA is based on 588 isolates

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 seen in Tables 3 and 4, the percent CA and EA was 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 were no major or very major errors which are acceptable.

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. aureus* (MRSA)**					
VIZION[a]	252	0	79	137	36	0
		(31.4%)		(54.4%)	(14.3%)	
OptiRead	252	0	46	144	58	4
		(18.3%)		(57.1%)	(24.6%)	
	***S. aureus* (MSSA)**					
VIZION	248	0	37	170	40	1
		(14.9%)		(68.6%)	(16.5%)	
OptiRead[b]	248	0	35	123	79	11
		(14.1%)		(49.6%)	(36.3%)	
	E. faecalis					
VIZION[c]	65	0	9	35	21	0
		(13.9%)		(53.9%)	(32.3%)	
OptiRead	65	0	22	29	13	0
		(33.9%)		(44.6%)	(21.5%)	

[a]Difference between the higher and lower dilutions for VIZION/MRSA is:-17.06%; 95% C.I. (-24.13% to -9.79%)
[b]Difference between the higher and lower dilutions for OptiRead/MSSA is: 22.18%; 95% C.I. (14.65% to 29.40 %)
[c]Difference between the higher and lower dilutions for VIZION/*E. faecalis* is:18.46%; 95% C.I. (3.95% to 32.13%)
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 performance between the Vision and OptiRead for the organisms listed and particularly for MRSA. The data for MRSA demonstrates a trend for one doubling dilution lower for results read by the VIZION compared to the reference method. Although there were no very major errors for this drug/organism combination in the clinical or challenge studies, there is concern that they may occur given this trending. As a result, the following footnote was included in the interpretation of results section of the package insert:

> *Delafloxacin MIC values for methicillin resistant S. aureus (MRSA) tended to be one doubling dilution lower with the VIZION as compared to the reference microdilution method. Therefore, consider alternative testing if an MIC of 0.25 µg/mL is obtained for MRSA isolates that were read by the VIZION.*

In addition, data demonstrated a trend of one doubling dilution higher compared to the reference method for results read by the OptiRead for MSSA and VIZION for *E. faecalis*. As a result, the following footnote was included in the interpretation of results section of the package insert:

> *Delafloxacin MIC values for methicillin susceptible S. aureus (MSSA) tended to be one doubling dilution higher with the OptiRead as compared to the reference microdilution method. In addition, MIC values interpreted by the VIZION tended to be one doubling dilution higher compared to the reference microdilution method for E. faecalis.*

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. aureus (MRSA and MSSA)	≤0.25	0.5	≥1
S. haemolyticus	≤0.25	0.5	≥1
E. faecalis	≤0.12	0.25	≥0.5

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.