510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K181946

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Plazomicin at concentrations 0.06-128 µg/mL to the Sensititre 18-24 MIC for susceptibility testing of non-fastidious Gram negative organisms.

C. Measurand:

Plazomicin 0.06-128 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 Plazomicin in the dilution range of 0.06-128 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 Plazomicin in the dilution range of 0.06 - 128 µg/mL for testing non-fastidious Gram negative organisms on the Sensititre 18-24 hour MIC panel.

   Plazomicin 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
   Proteus mirabilis
   Enterobacter cloacae

   The following *in vitro* data are available, but their clinical significance is unknown:

   Citrobacter freundii
   Citrobacter koseri
   Klebsiella aerogenes
   Klebsiella oxytoca
   Morganella morganii
   Proteus vulgaris
   Providentia stuartii
   Serratia marcescens

3. Special conditions for use statement(s):

For prescription use only

The following information is included in labeling:

- Studies of plazomicin were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing plazomicin has not been evaluated.

- The ability of the Sensititre system to detect resistance to Plazomicin in the following species is unknown because resistant strains were not available at the time of comparative testing: *E. cloacae, P. vulgaris, K. oxytoca, K. aerogenes*, and *C. koseri*. Isolates yielding Plazomicin MIC results suggestive of a resistant category (i.e., ≥8 µg/mL) should be submitted to a reference laboratory for further testing.

- Resistance mechanism characterization was not provided for all organisms at the time comparative testing, and therefore the performance of the Sensititre Plazomicin for non-fastidious gram negative organisms is unknown for isolates with the following resistance mechanisms: aminoglycoside modifying enzymes (AMEs), 16S rRNA methyltransferases (RMTs), up-regulation of efflux pumps, or loss of outer membrane porins.

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

- The safety and efficacy of plazomicin in treating clinical infections due to bacteria other than *E. coli, K. pneumoniae, P. mirabilis,* and *E. cloacae* may or may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information in those instances is unknown.

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, Ceftazidime/avibactam

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

   K152774

3. Comparison with predicate:

Table 1. Comparison with Predicate Device

Similarities		
Item	Sensititre 18-24 Susceptibility, Plazomicin (K181946)	Predicate: Sensititre 18-24 Susceptibility, Ceftazidime/avibactam (K152774)
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*	Same
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
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, Plazomicin (K181946)	Predicate: Sensititre 18-24 Susceptibility, Ceftazidime/avibactam (K152774)
Drug	Plazomicin (0.06-128 µg/mL)	Ceftazidime/avibactam (0.015/4-32/4 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 13 Gram negative organisms that included five *E. coli* isolates, four *K. pneumoniae* isolates, one *P. mirabilis*, one *E. cloacae* isolate, and two isolates of *K. oxytoca*. The isolates were tested in triplicate over three different days for each reading method (i.e., VIZION and OptiRead) for a total of 117 data points for each. 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 CLSI recommended QC strains, 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 were acceptable.

Table 2. Quality Control Results – Plazomicin

Organism	Conc. (µg/mL)	Reference Panel	OptiRead	VIZION
E. coli ATCC 25922 Expected Result: 0.25-2 µg/mL	0.12	0	0	0
	0.25	5	2	2
	0.5	68	70	71
	1	7	7	6
	2	0	1	1
	4	0	0	0
P. aeruginosa ATCC 27853 Expected Result: 1-4 µg/mL	0.5	0	0	0
	1	24	18	4
	2	53	62	72
	4	3	0	4
	8	0	0	0

Inoculum Density Check:

The inoculum density of each quality control, reproducibility, all clinical and challenge isolates were determined each day of testing. The inoculum was prepared to achieve turbidity equivalent to a 0.5 McFarland standard. A total of 453 inoculum density checks were performed for each test and reference panel for clinical isolates, 93 for each for test and reference panel for challenge isolates, 160 for each test and

reference panel for QC isolates, and all reproducibility isolates. 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 453 fresh clinical *Enterobacteriaceae* isolates that included *E. coli* (104), *K. pneumoniae* (84), *E. cloacae* (41), *P. mirabilis* (43), *P. vulgaris* (20), *K. oxytoca* (43), *M. morganii* (20), *K. aerogenes* (20), *C. koseri* (21), *C. freundii* (20), *P. stuartii* (16), and *S. marcescens* (21).

Challenge:

An additional 93 stock challenge isolates were tested at one study site. Challenge testing was conducted using *E. coli* (13), *K. pneumoniae* (23), *E. cloacae* (7), *P. mirabilis* (4), *P. vulgaris* (4), *K. oxytoca* (6), *M. morganii* (8), *K. aerogenes* (8), *C. koseri* (3), *C. freundii* (6), *P. stuartii* (3), and *S. marcescens* (8). Of these 93 challenge isolates, 11 were resistant to plazomicin by the reference method.

A total of 27 resistant strains (clinical and challenge) of *Enterobacteriaceae* were evaluated. No resistant strains of the following species were evaluated: *E. cloacae, P. vulgaris, K. oxytoca, E. aerogenes, C. koseri*, and *C. freundii*. In addition, only one isolate each of *P. mirabilis* and *S. marcescens* was resistant. As a result, the sponsor included the following limitation in the device labeling:

The ability of the Sensititre system to detect resistance to plazomicin in the following species is unknown because resistant strains were not available or insufficient at the time of comparative testing: E. cloacae, P. vulgaris, P. mirabilis, K. oxytoca, E. aerogenes, C. koseri, C. freundii, and *S. marcescens*.

In total, 546 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 *Enterobacteriaceae* isolates – Read by OptiRead*

Plazomicin	Total	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min	maj	vmj
Clinical	453	450	99.3	450	447	99.3	435	96.0	12	18	0	0
Challenge	93	92	98.9	87	86	98.9	88	94.6	15	5	0	0
All Organisms	546	542	99.3	537	533	99.3	523	95.8	27	23	0	0

*See legend for abbreviations under Table 4.

Table 4. Combined (Clinical and Challenge) Performance Summary of *Enterobacteriaceae* isolates – Read by VIZION

Plazomicin	Total	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#R	min	maj	vmj
Clinical	453	451	99.6	450	448	99.6	437	96.5	12	16	0	0
Challenge	93	92	99.0	87	86	98.9	88	94.6	15	5	0	0
All Organisms	546	543	99.5	537	534	99.4	525	96.2	27	21	0	0

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 were 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 no notable differences in EA or CA.

MIC Trends:

Table 5. Summary of Evaluation of MIC Trends (Combined Clinical and Challenge Data)

Plazomicin	Total	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
	E. coli					
VIZION[a]	114	0	16	67	31	0
		(14.04%)		(58.77%)	(27.19%)	
OptiRead[b]	114	0	16	69	29	0
		(14.04%)		(60.53%)	(25.44%)	
	K. pneumoniae					
VIZION[c]	107	0	10	75	22	0
		(9.35%)		(70.09%)	(20.56%)	
OptiRead[d]	107	0	11	78	18	0
		(10.28%)		(72.90%)	(16.82%)	
	E. cloacae					
VIZION[e]	48	0	3	34	11	0
		(6.25%)		(70.83%)	(22.92%)	
OptiRead[f]	48	0	3	37	8	0
		(6.25%)		(77.08%)	(16.67%)	
	P. mirabilis					
VIZION[g]	46	2	19	24	1	0
		(45.65%)		(52.17%)	(2.17%)	
OptiRead[h]	46	2	19	24	1	0
		(45.65%)		(52.17%)	(2.17%)	
	P. vulgaris					
VIZION[i]	24	0	16	7	1	0
		(66.67%)		(29.17%)	(4.17%)	
OptiRead[j]	24	1	17	6	0	0
		(75.00%)		(25.00%)	(0%)	
	K. oxytoca					
VIZION[k]	49	0	3	30	16	0
		(6.12%)		(61.22%)	(32.65%)	
OptiRead[l]	49	0	4	32	13	0
		(8.16%)		(65.31%)	(26.53%)	
	E. aerogenes					
VIZION[m]	28	0	3	19	6	0
		(10.71%)		(67.86%)	(21.43%)	
OptiRead[n]	28	0	5	17	6	0
		(17.86%)		(60.71%)	(21.43%)	
	C. koseri					
VIZION[o]	24	0	4	13	7	0
		(16.67%)		(54.17%)	(29.17%)	
OptiRead[p]	24	0	5	14	5	0
		(16.67%)		(58.33%)	(20.83%)	
	C. freundii					
VIZION[q]	26	0	3	18	5	0
		(11.54%)		(69.23%)	(19.23%)	
OptiRead[r]	26	0	3	20	3	0
		(11.54%)		(76.92%)	(11.54%)	
	M. morganii					
VIZION[s]	27	1	8	16	2	0

		(33.33%)		(59.26%)	(7.41%)	
OptiRead[t]	27	1	10	14	2	0
		(37.04%)		(51.85%)	(7.41%)	
	P. stuartii					
VIZION[u]	19	0	5	11	3	0
		(26.32%)		(57.89%)	(15.79%)	
OptiRead[v]	19	0	5	12	2	0
		(26.32%)		(63.16%)	(10.53%)	
	S. marcescens					
VIZION[w]	29	0	13	15	1	0
		(44.83%)		(51.72%)	(3.45%)	
OptiRead[x]	29	0	14	14	1	0
		(48.28%)		(48.28%)	(3.45%)	
	All *Enterobacteriaceae*					
VIZION[y]	541	3	103	329	106	0
		(19.59%)		(60.81%)	(19.59%)	
OptiRead[z]	541	4	112	337	88	0
		(21.44%)		(62.29%)	(16.27%)	

[a]Difference between the higher and lower dilutions for VIZION/*E. coli* is: 13.16%; 95% C.I. (2.64% to 23.39%)

[b]Difference between the higher and lower dilutions for OptiRead/ *E. coli* is: 11.40%; 95% C.I. (1.04% to 21.55%)

[c]Difference between the higher and lower dilutions for VIZION/*K. pneumoniae* is: 11.21%; 95% C.I. (1.61% to 20.79%)

[d]Difference between the higher and lower dilutions for OptiRead/ *K. pneumoniae* is: 6.54%; 95% C.I. (-2.77% to 15.88%)

[e]Difference between the higher and lower dilutions for VIZION/*E. cloacae* is: 16.67%; 95% C.I. (2.37% to 30.89%)

[f]Difference between the higher and lower dilutions for OptiRead/*E. cloacae* is: 10.42%; 95% C.I. (-2.83% to 23.96%)

[g]Difference between the higher and lower dilutions for VIZION/*P. mirabilis* is: -43.48%; 95% C.I. (-57.76% to -27.16%)

[h]Difference between the higher and lower dilutions for VIZION/*P. mirabilis* is: -43.48%; 95% C.I. (-57.76% to -27.16%)

[i]Difference between the higher and lower dilutions for VIZION/*P. vulgaris* is: -62.50%; 95% C.I. (-78.24% to -36.87%)

[j]Difference between the higher and lower dilutions for OptiRead/ *P. vulgaris* is: -75.00%; 95% C.I. (-88.00% to -50.78%)

[k]Difference between the higher and lower dilutions for VIZION/*K. oxytoca* is: -26.53%; 95% C.I. (11.07% to 41.07%)

[l]Difference between the higher and lower dilutions for OptiRead/ *K. oxytoca* is: 18.37%; 95% C.I. (3.27% to 32.96%)

[m]Difference between the higher and lower dilutions for VIZION/*E. aerogenes* is: 10.71%; 95% C.I. (-9.22% to 30.13%)

[n]Difference between the higher and lower dilutions for OptiRead/ *E. aerogenes* is: 3.57%; 95% C.I. (-17.41% to 24.25%)

[o]Difference between the higher and lower dilutions for VIZION/*C. koseri* is: 12.50%; 95% C.I. (-11.40% to 34.86%)

[p]Difference between the higher and lower dilutions for OptiRead/ *C. koseri* is: 4.17%; 95% C.I. (-18.25% to 26.20%)

[q]Difference between the higher and lower dilutions for VIZION/*C. freundii* is: 7.69%; 95% C.I. (-12.78% to 27.80%)

[r]Difference between the higher and lower dilutions for OptiRead/ *C. freundii* is: 0%; 95% C.I. (-19.00% to 19.00%)

[s]Difference between the higher and lower dilutions for VIZION/*M. morganii* is: -25.93%; 95% C.I. (-

45.51% to -4.23%)
[t]Difference between the higher and lower dilutions for OptiRead/*M. morganii* is: -29.63%; 95% C.I. (-49.11% to -7.38%)
[u]Difference between the higher and lower dilutions for VIZION/*P. stuartii* is: -10.53%; 95% C.I. (-35.24% to 15.64%)
[v]Difference between the higher and lower dilutions for OptiRead/*P. stuartii* is: -15.79%; 95% C.I. (-39.51% to 9.63%)
[w]Difference between the higher and lower dilutions for VIZION/*S. marcescens* is: -41.38%; 95% C.I. (-59.23% to -19.98%)
[x]Difference between the higher and lower dilutions for OptiRead/*S. marcescens* is: -44.83%; 95% C.I. (-62.35% to -23.06%)
[y]Difference between the higher and lower dilutions for VIZION/All *Enterobacteriaceae* is: 0%; 95% C.I. (-4.73% to 4.73%)
[z]Difference between the higher and lower dilutions for OptiRead/All *Enterobacteriaceae* is: -5.18%; 95% C.I. (-9.82% to -0.51%)

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 *P. mirabilis, P. vulgaris,* and *S. marcescens* isolates 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:

> *Plazomicin MIC values for P. mirabilis, P. vulgaris, and S. marcescens 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 Plazomicin are as listed in Table 6.

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

	Susceptible (S)	Intermediate (I)	Resistant (R)
*Enterobacteriaceae**	≤2	4	≥8

*Only *E. coli, K. pneumoniae, P. mirabilis,* and *E. cloacae* demonstrated effectiveness in clinical trials.

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

O. Conclusion:

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