

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY**

**A. 510(k) Number:**

K152774

**B. Purpose for Submission:**

Addition of Ceftazidime/Avibactam to the Sensititre 18-24 hours MIC or Breakpoint Susceptibility System for non-fastidious gram negative organisms.

**C. Measurand:**

Ceftazidime/Avibactam 0.015/4 – 32/4 µg/mL

**D. Type of Test:**

Quantitative Antimicrobial Susceptibility Test (AST) growth based

**E. Applicant:**

ThermoFisher Scientific

**F. Proprietary and Established Names:**

Sensititre Susceptibility plates

**G. Regulatory Information:**

1. Regulation section:

866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

Class II

3. Product code:

JWY – Manual Antimicrobial Susceptibility Test System

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

LTT - Panels, Test, Susceptibility, Antimicrobial

4. Panel: 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 Ceftazidime/Avibactam the dilution range of 0.015/4 – 32/4 µg/mL for testing non-fastidious gram negative organisms on the Sensititre 18-24 hour MIC panel.

The approved primary “Indications for Use” and clinical significance for non-fastidious gram negative isolates:

*Enterobacter cloacae*  
*Escherichia coli*  
*Klebsiella oxytoca*  
*Klebsiella pneumoniae*  
*Proteus mirabilis*  
*Citrobacter freundii*  
*Citrobacter koseri*  
*Enterobacter aerogenes*  
*Proteus spp.*  
*Pseudomonas aeruginosa*

3. Special conditions for use statement(s):

For prescription use only

The performance of Ceftazidime/avibactam with *Enterobacteriaceae* and *Pseudomonas aeruginosa* was established using the Autoinoculator/AIM autoinoculator. The use of an alternative inoculation system when testing Ceftazidime/avibactam has not been evaluated.

The ability of the Sensititre system to detect isolates that are resistant to Ceftazidime/Avibactam is unknown because a sufficient number of resistant isolates was not available at the time of the comparative testing. If such isolates are observed, they should be submitted to a reference lab.

Enzyme group characterization was not available for all organisms at the time of comparative testing, and therefore the performance of the Sensititre Ceftazidime/Avibactam for non-fastidious gram negative isolates is unknown for the following: *Enterobacteriaceae* (OXA) and *Pseudomonas aeruginosa* [AmpC, and loss of outer membrane porin (OprD)].

4. Special instrument requirements:

Sensititre AIM for device inoculation  
Sensititre Vizion or OptiRead for device 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 read manually by visual reading of growth or automatically on an OptiRead<sup>®</sup>/Autoreader<sup>®</sup> 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**

<b>Similarities</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
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 <i>Enterobacteriaceae</i> , <i>Pseudomonas aeruginosa</i> , and other non- <i>Enterobacteriaceae</i> and of non-fastidious Gram positive isolates, comprising of <i>Staphylococcus spp.</i> , <i>Enterococcus spp.</i> , and Beta haemolytic <i>Streptococci</i> other than <i>S. pneumoniae</i>	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 negative isolates	Same
Results Reported	Report results as Minimum Inhibitory Concentration (MIC) and interpretive criteria (S, I, R)	Same
Read Method	Automated and Manual	Same

<b>Differences</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
Reading Method	Results can be read by the following methods: 1) Automatically - with the AutoReader/OptiRead (fluorogenic substrate technology) 2) On the Vizion - Digital Viewing Device 3) Manually - using a manual viewer via visual interpretation of growth	Organism growth/turbidity based reading and interpretation via manual read or MicroScan instrumentation (Walkaway, AutoScan-4)
Antimicrobial	Ceftazidime/Avibactam	Gatifloxacin
Incubation	18-24 hours	16-20 hours

## **K. Standard/Guidance Document Referenced:**

1. Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.
2. CLSI M100-S025: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement
3. CLSI M7-A9: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth 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 manually by visual reading of growth or by use of an automated reader.

The Sensititre autoreader systems (OptiRead<sup>®</sup>, Autoreader<sup>®</sup>) utilize 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 (if/when applicable):**

### 1. Analytical performance:

#### *a. Precision/Reproducibility:*

A reproducibility study was performed using 25 isolates of non-fastidious gram negative rods (5 *E.coli*, 4 *K. pneumoniae*, 3 *K. oxytoca*, 2 *E. cloacae*, 2 *E. aerogenes*, 2 *C. koseri*, 3 *Citrobacter freundii*, 2 *P. mirabilis*, 1 *Proteus spp.*, and 1 *P. aeruginosa*). The Sensititre AIM was used for plate inoculation. The isolates were tested one time at each of three sites for each reading method (Vizion, OptiRead). The mode MIC value was determined and the reproducibility was calculated based on MICs falling within  $\pm 1$  dilution of the mode MIC value. The testing resulted in the overall “best-case” reproducibility results of greater than 95% for both the manual and

autoreader methods.

b. *Linearity/assay reportable range:*

Not Applicable

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

Organisms recommended by both FDA (CDER) and The CLSI, namely *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, and *Pseudomonas aeruginosa* ATCC 27853, were tested against Ceftazidime/Avibactam. Quality control testing was performed at all study sites using the Sensititre AIM for inoculation, read by the Sensititre Vizion and the Sensititre OptiRead. The following table represents the frequency of the results. All results were within acceptable range.

**Table 2. Quality Control Results – Ceftazidime/Avibactam**

<i>ORGANISM</i>	Conc. <sup>a</sup> (µg/mL)	Reference Panel	Sensititre OptiRead	Sensititre Vizion
<i>Escherichia coli</i> ATCC 25922 (0.06-0.5 µg/mL)	0.03	0	0	0
	0.06	8	9	13
	0.12	35	34	33
	0.25	17	17	14
	0.5	0	0	0
	1	0	0	0
<i>Escherichia coli</i> ATCC 35218 (0.03-0.12 µg/mL)	0.015	0	0	0
	0.03	1	10	5
	0.06	56	48	50
	0.12	3	2	5
	0.25	0	0	0
<i>Pseudomonas aeruginosa</i> ATCC 27853 (0.5-4 µg/mL)	0.25	0	0	0
	0.5	1	16	10
	1	49	44	42
	2	9	0	8
	4	1	0	0
	8	0	0	0
<i>Klebsiella pneumoniae</i> ATCC 700603 (0.25-2 µg/mL)	0.12	0	0	0
	0.25	0	9	8
	0.5	49	46	48
	1	11	5	4
	2	0	0	0
	4	0	0	0

<i>Klebsiella pneumoniae</i> <sup>b</sup> ATCC 700603 (>16 µg/mL)	<16	0	0	0
	>16	60	60	60

<sup>a</sup>MIC for ceftazidime in the presence of a fixed concentration of 4 mg/L of avibactam.

<sup>b</sup>*K. pneumoniae* ATCC 700603 should be tested against ceftazidime and avibactam and ceftazidime alone to confirm the activity of avibactam in the combination and to ensure that the plasmid encoding the beta-lactamase has not been lost in this strain. The acceptable range for ceftazidime alone is greater than 16 mg/L.

The inoculum density of the quality control organisms tested was determined each day of testing. A total of 214 inoculum density checks were performed. The average colony counts of each quality control organism at each site 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 CLSI microbroth dilution 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 testing was conducted at three sites using 269 non-fastidious gram negative rods of the *Enterobacteriaceae* family (60 *E. coli*, 30 *K. pneumoniae*, 30 *K. oxytoca*, 30 *E. cloacae*, 29 *E. aerogenes*, 15 *C. koseri*, 30 *C. freundii*, 30 *P. mirabilis*, and 15 *Proteus spp.*) and 60 isolates of *P. aeruginosa* totaling 329 fresh clinical isolates tested. Additional testing of challenge isolates was conducted at one study site. Challenge testing was conducted using 88 non-fastidious gram negative rods of the *Enterobacteriaceae* family (15 *E. coli*, 18 *K. pneumoniae*, 14 *K. oxytoca*, 5 *E. cloacae*, 5 *E. aerogenes*, 5 *C. koseri*, 10 *C. freundii*, 11 *P. mirabilis*, and 5 *Proteus spp.*) and 5 isolates of *P. aeruginosa* totaling 93 stock challenge isolates tested.

The growth rates for the Vizion and OptiRead methods were both greater than 90%. Table 3 and Table 4 below illustrate performance based on essential agreement and category agreement of clinical and challenge isolates for both *P. aeruginosa* and the *Enterobacteriaceae* family. Table 3 illustrates performance using the Vizion and Table 4 illustrates performance using the OptiRead.

**Table 3. Performance Summary of Gram Negative Organisms - Read by Vizion**

Ceftazidime /Avibactam	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	%CA	#R	maj (%)	vmj (%)
<i>Enterobacteriaceae</i>											
Clinical	269	269	100	262	262	100	268	99.6	1	0	1 (100%)
Challenge	88	88	100	84	84	100	88	100	0	0	0
Combined	357	357	100	346	346	100	356	99.7	1	0	1(100%)
<i>Pseudomonas aeruginosa</i>											
Clinical	60	60	100	59	59	100	59	98.3	2	0	1 (50%)
Challenge	5	5	100	4	4	100	5	100	1	0	0
Combined	65	65	100	63	63	100	64	98.5	3	0	1 (33%)
<b>Combined Total</b>											
<b>TOTAL</b>	<b>422</b>	<b>422</b>	<b>100</b>	<b>409</b>	<b>409</b>	<b>100</b>	<b>420</b>	<b>99.5</b>	<b>4</b>	<b>0</b>	<b>2 (50%)</b>

**Table 4. Performance Summary of Gram Negative Organisms - Read by OptiRead**

Ceftazidime /Avibactam	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	%CA	#R	maj (%)	vmj (%)
<i>Enterobacteriaceae</i>											
Clinical	269	269	100	259	259	100	268	99.6	1	0	1 (100%)
Challenge	88	88	100	84	84	100	87	98.9	0	1 (1.1%)	0
Combined	357	357	100	343	343	100	355	99.4	1	1 (0.3%)	1 (100%)
<i>Pseudomonas aeruginosa</i>											
Clinical	60	60	100	59	59	100	59	98.3	2	0	1 (50%)
Challenge	5	5	100	4	4	100	5	100	1	0	0
Combined	65	65	100	63	63	100	64	98.5	3	0	1 (33%)
<b>Combined Total</b>											
<b>TOTAL</b>	<b>422</b>	<b>422</b>	<b>100</b>	<b>406</b>	<b>406</b>	<b>100</b>	<b>419</b>	<b>99.3</b>	<b>4</b>	<b>1 (0.2%)</b>	<b>2 (50%)</b>

EA - Essential Agreement

CA - Category Agreement

R- resistant isolates

maj – major discrepancies

vmj- very major discrepancies

Note: There are no minor error calculations due to lack of intermediate interpretive criteria

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 (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel result.

In each instance, both the percent CA and percent EA consistently fell 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 manual and autoread methods revealed very little difference.

Two very major discrepancies were observed with the Vizion read method (involving one resistant isolate of *K. pneumoniae* and one resistant isolate of *P.aeruginosa*). However taking into consideration the lack of an intermediate breakpoint for ceftazidime/avibactam, FDA examined the MIC data associated with those discrepancies to determine if the values fall within essential agreement compared to reference. The data showed that both very major discrepancies fall within essential agreement of the reference method MIC result, and FDA considers these findings acceptable.

Similarly, two very major discrepancies and one major discrepancy were observed with the OptiRead method (involving one resistant isolate of *P. aeruginosa*, one resistant isolate of *K. pneumoniae*, and one susceptible isolate of *E. coli*, respectively). However taking into consideration the lack of an intermediate breakpoint for ceftazidime/avibactam and the fact that all discrepancies fall within essential agreement of the reference method MIC result, FDA considers these findings acceptable.

Ceftazidime/avibactam performance data was also evaluated for any signs of MIC result trends as illustrated in Table 5 below.

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

Ceftazidime/ Avibactam	Total	2 dil. lower	1 dil. lower	Exact	1 dil. higher	2 dil. higher
<i>Enterobacteriaceae</i>						
Vizion	357	0	16.5% (59/357)	50.4% (180/357)	33.1% (118/357)	0
OptiRead	357	0	20.7% (74/357)	46.2% (165/357)	33.1% (118/357)	0
<i>Pseudomonas aeruginosa</i>						
Vizion	65	0	30.8% (20/65)	61.5% (40/65)	7.7% (5/65)	0
OptiRead	65	0	33.8% (22/65)	55.4% (36/65)	10.8% (7/65)	0

As illustrated in Table 5, there was no marked difference in device performance between Vizion and OptiRead methods. However, a difference between organism groups is apparent. The data for the *Enterobacteriaceae* group demonstrates an upward trend of one doubling dilution in the MIC of ceftazidime/avibactam on the Sensititre panel as compared to that of the reference method 33.1% of the time, for both Vizion and OptiRead methods. This upward trend resulted in only one major discrepancy since the majority of the organisms tested had MIC values which fell well below the susceptible MIC breakpoint of 8/4 µg/mL.

Moreover, the data for *Pseudomonas aeruginosa* demonstrates a downward trend of one doubling dilution in the MIC of ceftazidime/avibactam on the Sensititre panel as

compared to that of the reference method 30.8% and 33.8% of the time, for Vizion and OptiRead methods respectively. This downward trend resulted in only one very major discrepancy since the majority of the organisms tested had MIC values which fell well below the susceptible MIC breakpoint of 8/4 µg/mL.

The following footnote was added to the device performance table in the package insert to inform end users of observed trending:

*Sensititre ceftazidime/avibactam MIC values for non-fastidious Enterobacteriaceae isolates tended to trend upward one doubling dilution compared to the reference broth microdilution method. Sensititre ceftazidime/avibactam MIC values for Pseudomonas aeruginosa isolates tended to trend downward one doubling dilution as compared to the reference broth microdilution method. The trending was observed with the use of both OptiRead and Vizion read methods.*

b. *Matrix comparison:*

Not Applicable

3. Clinical studies:

a. *Clinical Sensitivity:*

Not Applicable

b. *Clinical specificity:*

Not Applicable

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

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria (ug/mL) for susceptible(S) and resistant (R) as listed below were used to evaluate all performance data.

*Enterobacteriaceae*                      S ≤ 8/4, R ≥ 16/4

*Pseudomonas aeruginosa*            S ≤ 8/4, R ≥ 16/4

**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.