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

A. 510(k) Number:

K150556

B. Purpose for Submission:

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

C. Measurand:

Ceftolozane/Tazobactam 0.03/4 - 64/4 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 non-fastidious Gram positive isolates, comprising of *Staphylococcus* spp., *Enterococcus* spp., and Beta hemolytic *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 Ceftolozane/Tazobactam in the dilution range of 0.03/4 - 64/4 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
   Pseudomonas aeruginosa

3. Special conditions for use statement(s):

   For prescription use only

   The ability of the Sensititre system to detect non-susceptible isolates to Ceftolozane/Tazobactam is unknown because non-susceptible isolates were 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 some organisms at the time of comparative testing, and therefore the performance of Sensititre Ceftolozane/Tazobactam for non-fastidious gram negative isolates is unknown for the following:
   Enterobacteriaceae (*OXA*); *Pseudomonas aeruginosa* (chromosomal *AmpC*, loss of *OprD*, up-regulation of *MexXY*, and *MexAB*).

4. Special instrument requirements:

   Sensititre Vizion or OptiRead
   Sensititre AIM for inoculation

I. Device Description:

Sensititre MIC Susceptibility plate MIC panels are multi-well plastic micro-titer plates, precision 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.

AST results may be read automatically using Sensititre AutoReader/OptiRead /ARIS; manually using the Sensititre manual viewer/Vizion.

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	Device Sensititre 18- 24 hours MIC or Breakpoint Susceptibility System for non-fastidious Organisms	Predicate MicroScan Dried Gram-Negative and Gram-Positive MIC/Combo Panels (K010159)
Intended Use	The Sensititre MIC and Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious organisms	To determine quantitative and/or qualitative antimicrobial agent susceptibility
Test organism	Non-fastidious gram negative isolates from culture	Same
Results reported	Report results as Minimum Inhibitory Concentration (MIC) and interpretative criteria (S, I, R)	Same
Type of test	Automated or manual	Same

Differences		
Item	Device	Predicate
Antimicrobial	Ceftolozane/Tazobactam	Gatifloxacin
Reading Method	Results can be read by two different methods: 1) Automatically on the AutoReader/Optiread using fluorescence 2) On the Vizion Device 3) Using a manual viewer, by visual reading of growth.	Organism turbidity growth visually or by MicroScan instrumentation
Incubation	18- 24hours	16-20 hours

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

1. The FDA guidance document: Guidance for Industry and FDA Staff- Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems

2. CLSI M100-S25: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement (QC parameters only)

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 doubling dilution of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read manually by visual reading of growth or automatically on an autoreader via fluorescence.

The Sensititre OptiRead System 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 non-fluorescent (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 the 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:

Reproducibility study was performed using 25 strains of *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Enterobacter cloacae, Proteus mirabilis* and *Pseudomonas aeruginosa*. Sensititre AIM was used for inoculation. The organisms 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 ± 1 dilution of the mode MIC value. The testing resulted in overall reproducibility of greater than 95% for both manual and automated read methods. The results were acceptable.

To specifically address reproducibility using isolates with defined enzyme groups, an additional reproducibility study of ten *Enterobacteriaceae* spp. was conducted in triplicates for three days at 2 sites. The isolates were *E. coli, K. pneumoniae, K. oxytoca,* and *P. mirabilis*. There were four ESBLs, three CTX-M, seven TEM, and five SHV enzyme groups from these isolates. Some of these isolates may produce multiple enzymes. OXA was not included in this reproducibility study. The testing resulted in overall reproducibility of greater than 95% for both manual and automated read methods. The results were acceptable.

b. Linearity/assay reportable range:

Not Applicable

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

Organisms recommended by both the 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 Ceftolozane/Tazobactam. Quality control testing was performed at all study sites using the Sensititre AIM for inoculation, read by Sensititre Vizion and the Sensititre OptiRead. The following table represents the frequency of the results and all results were in acceptable range.

Table 2: Ceftolozane/Tazobactam QC results by Sensititre OptiRead and Vizion

ORGANISM	**Conc. (µg/mL)**	**Reference**	**Sensititre OptiRead**	**Sensititre Vizion**
E. coli ATCC 25922 Expected Range 0.12/4- 0.5/4µg/mL	0.06/4			
	0.12/4	24	7	10
	0.25/4	34	51	45
	0.5/4	2	2	5

	1/4			
E. coli ATCC 35218 Expected Range 0.06/4- 0.25/4µg/mL	0.03/4			
	0.06/4	18		1
	0.12/4	38	58	53
	0.25/4	4	2	6
	0.5/4			
K. pneumoniae ATCC 700603 Expected Range 0.5/4- 2/4µg/mL	0.25/4			
	0.5/4	7	3	3
	1/4	52	53	52
	2/4	1	4	5
	4/4			
P. aeruginosa ATCC 27853 Expected Range 0.25/4- 1/4µg/mL	0.12/4			
	0.25/4	32	13	14
	0.5/4	27	45	43
	1/4	1	2	3
	2/4			

The inoculum density of the quality control organisms was determined each day of testing. A total of 214 inoculum density checks were performed; the average colony counts of each QC strain at each site were within the recommended range.

An additional QC study was conducted during in-house study as part of the additional reproducibility/challenge study. The frequency of results listed below. Results were in acceptable range:

Table 3: Additional Ceftolozane/Tazobactam QC results by Sensititre OptiRead and Vizion

ORGANISM	**Conc. (µg/mL)**	**Reference**	**Sensititre OptiRead**	**Sensititre Vizion**
E. coli ATCC 25922 Expected Range 0.12/4- 0.5/4µg/mL	0.06/4			
	0.12/4			
	0.25/4	2		
	0.5/4		2	2
	1/4			
E. coli ATCC 35218 Expected Range 0.06/4- 0.25/4µg/mL	0.03/4			
	0.06/4			
	0.12/4	2	2	2
	0.25/4			
	0.5/4			

K. pneumoniae ATCC 700603 Expected Range 0.5/4- 2/4µg/mL	0.25/4			
	0.5/4			
	1/4	2	2	2
	2/4			
	4/4			
P. aeruginosa ATCC 27853 Expected Range 0.25/4- 1/4µg/mL	0.12/4			
	0.25/4			
	0.5/4	2	2	
	1/4			2
	2/4			

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 recommended broth microdilution reference plate was prepared according to CLSI recommendation. Clinical testing was performed on 230 *Enterobacteriaceae* (i.e. *E. coli, K. pneumoniae, K. oxytoca, Enterobacter cloacae,* and *Proteus mirabilis*), and 70 *P. aeruginosa* at three sites and Sensititre AIM auto-inoculator was used as the inoculation method. They were fresh clinical isolates and all grew. The challenge set included 65 *Enterobacteriaceae* and ten *P. aeruginosa.* An additional challenge study of 23 *Enterobacteriaceae* isolates with enzyme characterization was conducted. The enzyme groups were distributed as follows: (18) ESBL, (6) CTX-M, (15) TEM, and (12) SHV. Isolates with the following enzyme groups were not available for testing: *Enterobacteriaceae* isolates with known OXA enzymes and *Pseudomonas aeruginosa* with known chromosomal AmpC, loss of OprD, or up-regulation of MexXY, and MexAB. A limitation was included in labeling.

The performance is shown in the tables 4 and 5.

Table 4: Performance Summary of Gram Negative Organisms - Read by Vizion

Ceftolozane/ Tazobactam	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA%	#R	min	maj	vmj
	Enterobacteriaceae (≤2/4, 4/4, ≥8/4)											
Clinical	230	226	98.3	228	224	98.2	227	98.7	10	2	1	0
Challenge	65	63	97.0	62	60	96.8	63	97.0	7	2	0	0
Additional challenge	23	23	100	21	21	100	23	100	7	0	0	0
Subtotal	318	312	98.1	311	305	98.1	313	98.4	24	4	1	0
	P. aeruginosa (≤4/4, 8/4, ≥16/4)											
Clinical	70	70	100	70	70	100	69	98.6	0	1	0	0
Challenge	10	10	100	10	10	100	10	100	1	0	0	0
Subtotal	80	80	100	80	80	100	79	98.8	1	1	0	0
Total	**398**	**392**	**98.5**	**391**	**385**	**98.5**	**392**	**98.5**	**25**	**5**	**1**	**0**

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

EA is when there is agreement between the reference method and the Sensititre panel within plus or minus one serial two-fold dilution of antibiotic. Category agreement (CA) is when the Sensititre panel result interpretation agrees exactly with the reference panel result interpretation. Evaluable EA is when the MIC result is on scale for both the Sensititre and the reference and have on-scale EA. The EA% is acceptable when compared to the reference method as described in the FDA guidance document, "Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA".

Table 5: Performance Summary of Gram Negative Organisms - Read by OptiRead

Ceftolozane/ Tazobactam	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA%	#R	min	maj	vmj
	Enterobacteriaceae (≤2/4, 4/4, ≥8/4)											
Clinical	230	227	98.7	228	225	98.7	226	98.3	10	3	1	0
Challenge	65	64	98.5	62	61	98.4	64	98.5	7	1	0	0
Additional challenge	23	23	100	21	21	100	23	100	7	0	0	0
Subtotal	318	314	98.7	311	307	98.7	313	98.4	24	4	1	0
	P. aeruginosa (≤4/4, 8/4, ≥16/4)											
Clinical	70	70	100	70	70	100	69	98.6	0	1	0	0
Challenge	10	10	100	10	10	100	10	100	1	0	0	0
Subtotal	80	80	100	80	80	100	79	98.8	1	1	0	0
Total	**398**	**394**	**99.0**	**391**	**387**	**99.0**	**392**	**98.5**	**25**	**5**	**1**	**0**

Tables 4 and 5 above demonstrated acceptable EA% with both manual and automated reads when comparing to the reference method as described in the FDA guidance document, "Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA".

Using the data provided by the sponsor in the diagonal table format as recommended in the AST Guidance, an analysis was conducted to evaluate MIC values trending in Table 6 below:

Table 6: Summary of Trending Evaluation

Ceftolozane/ Tazobactam	Total	2 dil. lower	1 dil. lower	Exact	1 dil. higher	2 dil. higher
	Enterobacteriaceae					
Vizion	318	0	5.0% (16/318)	34.9% (111/318)	58.2% (185/318)	1.9% (6/318)
OptiRead	318	0.3% (1/318)	6.0% (19/318)	36.8% (117/318)	56.0% (178/318)	0.9% (3/318)
	P. aeruginosa					
Vizion	80	0	2.5% (2/80)	61.3% (49/80)	36.3% (29/80)	0
OptiRead	80	0	7.5% (6/80)	63.8% (51/80)	28.8% (23/80)	0

The data in Table 6 demonstrated there was no difference between manual and automated read when Vizion and OptiRead were used respectively. However, there was difference between organism groups. For *Enterobacteriaceae* organisms, it was one doubling dilution higher 55% of the time; for exact agreement, it was below 50% at 35% when comparing to the CLSI reference method. It only caused one major discrepancy since the majority of the susceptible strains were much below the susceptible breakpoints of ≤2/4 (ranged from 0.12/4 to 0.5/4 µg/mL). The CA for both reading methods was high at 98.4%. For *Pseudomonas aeruginosa,* it was in exact agreement about 60% of the time, with 36.3% and 28.8% one doubling-dilution higher for manual and automated read respectively. There were 25 resistant organisms tested, with no very major discrepancies observed. Eleven of the resistant isolates were from *E. coli* or *K. pneumoniae.*

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 interpretative criteria (µg/ml) for S, I, R as listed below, were used to evaluate all performance data.

Enterobacteriaceae	≤2/4, 4/4, ≥8/4
Pseudomonas aeruginosa	≤4/4, 8/4, ≥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.