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

A. 510(k) Number:

K173209

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of meropenem/vaborbactam at concentrations of 0.008/8 – 16/8 µg/mL to the Sensititre 18-24-hour MIC or Breakpoint Susceptibility System for testing gram-negative non-fastidious isolates.

C. Measurand:

Meropenem/vaborbactam in the dilution range of 0.008/8 – 16/8 µg/mL. The vaborbactam concentration is fixed at 8 µg/mL in this combination.

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 Meropenem/Vaborbactam in the dilution range of 0.008/8 – 16/8 µg/mL.

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product codes:

   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* sp., *Enterococcus* sp., 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 meropenem/vaborbactam in the dilution range of 0.008/8 – 16/8 µg/mL for testing non-fastidious gram negative organisms on the Sensititre 18 – 24 hour MIC panel.

   Meropenem/Vaborbactam 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 species complex

   The following in vitro data are available but their clinical significance is unknown.

   Citrobacter freundii
   Citrobacter koseri
   Enterobacter aerogenes
   Klebsiella oxytoca
   Morganella morganii

Proteus mirabilis
Providencia spp.
Serratia marcescens

3. Special conditions for use statement(s):

   For prescription use only

   The following limitations are included in the labeling:

   > *The performance of meropenem/vaborbactam with gram negative organisms was established using the AutoReader (OptiRead) and Vizion reading methods only. The use of an alternative reading method when testing meropenem/vaborbactam has not been evaluated.*
   >
   > *Studies of meropenem/vaborbactam with Enterobacteriaceae were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing meropenem/vaborbactam has not been evaluated.*
   >
   > *The ability of the Sensititre system to detect resistance to meropenem/vaborbactam in the following species is unknown because resistant strains were not available at the time of comparative testing: Enterobacter cloacae, Proteus mirabilis, Klebsiella oxytoca, Morganella morganii, Enterobacter aerogenes, Citrobacter koseri, Citrobacter freundii, Providencia spp.,* and *Serratia marcescens. Isolates yielding meropenem/vaborbactam MIC results suggestive of a resistant interpretive category (≥16/8 µg/mL) should be submitted to a reference laboratory for further testing.*

4. Special instrument requirements:
   Sensititre AIM for device inoculation
   Sensititre VIZION or OptiRead for plate reading

I. Device Description:

Sensititre MIC Susceptibility MIC panels are multi-well microtiter plates, dosed with dried, stabilized antimicrobials. It is a miniaturized version of the classic broth dilution method 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 growth using the digital device (VIZION) or automatically on an autoreader (OptiRead) using fluorescence.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Sensititre 18-24 hour Susceptibility System, Ceftazidime/Avibactam

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

   K152774

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	**Device (**K173209)	**Predicate (**K152774)
Device	Sensititre 18-24 hour Susceptibility System Meropenem/Vaborbactam	Sensititre 18-24 hour Susceptibility System, Ceftazidime/Avibactam
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* sp., *Enterococcus* sp., and Beta hemolytic *Streptococci* other than *S. pneumoniae.*	Same
Test Panel	96-well plate dosed with selected antimicrobial agents then dried	Same
Results	Automated and Manual	Same
Reading Methods	Results can be read using the following methods: 1) Automatically with the OptiRead (fluorescent substrate technology) 2) On the VIZION (digital viewing device)	Same
Test Organisms	Non-fastidious gram negative isolates	Same
Incubation	18-24 hours	Same

Differences		
Item	**Device**	**Predicate**
Antimicrobial agent	Meropenem/Vaborbactam	Ceftazidime/Avibactam

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

Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.

CLSI M100-S027: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh Informational Supplement

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 includes multi-well plastic microtiter 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 determine 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 (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   A reproducibility study was performed at four sites using 12 gram negative organisms that included *E. coli* (four isolates), *K. pneumoniae* (four isolates), *E. cloacae* (one isolate), *K. oxytoca* (two isolates), and *P. mirabilis* (one isolate). The isolates were tested in triplicate over three days with each read method (i.e., VIZION and OptiRead). The Sensititre Aim inoculator was used for plate inoculation. The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. Reproducibility was greater than 95% for both read methods.

b. *Linearity/assay reportable range:*

Not applicable

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

Quality control strains recommended by both FDA and the CLSI were tested with meropenem/vaborbactam at four sites. The QC organisms tested included *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 35218, *K. pneumoniae* ATCC 700603, and *K. pneumoniae* ATCC BAA 1705. The QC strains were tested a minimum of 20 times per site and read using the Vizion and OptiRead. For three QC strains the lowest dilution in the acceptable QC range (0.008/8) is the lowest dilution tested on the Sensititre panel; results for these strains may be reported as ≤0.008 µg/mL (off-scale). The sponsor included the following statement as a footnote to the QC table in the device labeling:

> *Meropenem/vaborbactam – the acceptable range of quality control for E. coli ATCC 25922 and E. coli ATCC 35218 is 0.008/8 – 0.06/8 µg/mL. The lowest dilution on the Sensititre panels is 0.008/8 µg/mL and off-scale MIC results (0.008/8 µg/mL) could occur.*

According to the CLSI document M100, Performance Standards for Antimicrobial Susceptibility Testing, the QC strain *P. aeruginosa* ATCC 27853 should be routinely tested for meropenem/vaborbactam. In addition, the sponsor provided the acceptable QC range for K. pneumoniae ATCC 1705 as provided in the CLSI M100 document. The sponsor included the following information in the QC table:

> *QC range for K. pneumoniae ATCC 1705 with meropenem/vaborbactam is 0.015/8 – 0.06/8 µg/mL.*
>
> *Test P. aeruginosa ATCC 27853 routinely for QC of meropenem/vaborbactam.*

The results demonstrate that the Sensititre 18-24 hour MIC or Breakpoint panel with meropenem/vaborbactam can produce quality control results in the recommended range > 95% of the time (Table 2).

Table 2. Quality Control Results for Sensititre 18 – 24 hour MIC or Breakpoint Susceptibility System with Meropenem/Vaborbactam with the VIZION and OptiRead Methods.

QC Organism	Meropenem/ vaborbactam Range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre	
				Read method	
				Vizion	OptiRead
E. coli ATCC 25922	0.008/8 –0.06/8	≤0.008/8	5	2	2
		0.015/8	47	77	78
		0.03/8	26	1	0
		0.06/8	2	0	0
		0.12/8	0	0	0
P. aeruginosa ATCC 27853	0.12/8 – 1/8	0.06/8	0	0	0
		0.12/8	27	15	1
		0.25/8	33	51	73
		0.5/8	13	12	3
		1/8	7	2	3
		2/8	0	0	0
E. coli ATCC 35218	0.008/8 –0.06/8	≤0.008/8	5	1	1
		0.015/8	49	78	78
		0.03/8	26	1	1
		0.06/8	0	0	0
		0.12/8	0	0	0
K. pneumoniae ATCC 700603	0.015/8 –0.06/8	≤0.008/8	3	0	0
		0.015/8	50	11	25
		0.03/8	25	77	63
		0.06/8	4	1	1
		0.12/8	0	0	0
K. pneumoniae ATCC BAA-1705	0.008/8 –0.06/8	≤0.008/8	9	1	2
		0.015/8	48	40	45
		0.03/8	17	35	30
		0.06/8	6	4	3
		0.12/8	0	0	0

Inoculum Density. Inoculum density checks were performed a sufficient number of times; all organism suspensions were in the acceptable range.

Purity checks. Purity checks were performed on all isolates following plate inoculation. Only results from pure cultures were evaluated.

Growth Failure: All isolates tested showed growth in the Sensititre panels.

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:

Results obtained with Sensititre 18 – 24 hour MIC or Breakpoint Susceptibility System with meropenem/vaborbactam were compared to results obtained with the CLSI broth microdilution reference panel. Clinical testing was performed at four sites using a total of 453 *Enterobacteriaceae* clinical isolates comprised of the following species: *C. freundii* (20 isolates), *C. koseri* (21 isolates), *E. coli* (104 isolates), *E. aerogenes* (20 isolates), *E. cloacae* (41 isolates), *K. oxytoca* (43 isolates), *K. pneumoniae* (84 isolates), *M. morganii* (20 isolates), *P. mirabilis* (43 isolates), *Providencia* spp. (36 isolates) and *S. marcescens* (21 isolates). All the clinical isolates were fresh isolates. 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 (manual read) and the OptiRead in a blinded manner. The sponsor added the following limitations to the device labeling to reflect these inoculation and read methods:

> *Studies of meropenem/vaborbactam with gram negative organisms were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing meropenem/vaborbactam has not been evaluated.*
>
> *The performance of meropenem/vaborbactam with gram negative organisms was established using the AutoReader (OptiRead) and Vizion reading methods only. The use of an alternative reading method when testing meropenem/vaborbactam has not been evaluated.*

A total of 108 *Enterobacteriaceae* challenge isolates were tested at a single site. Species tested included: *C. freundii* (6 isolates), *C. koseri* (5 isolates), *E. coli* (12 isolates), *E. aerogenes* (7 isolates), *E. cloacae* (8 isolates), *K. oxytoca* (6 isolates), *K. pneumoniae* (41 isolates), *M. morganii* (5 isolates), *P. mirabilis* (4 isolates), *Providencia* spp. (5 isolates) and *S. marcescens* (9 isolates).

For the *Enterobacteriaceae*, the results from clinical and challenge testing determined

with the VIZION demonstrated a combined EA of 97.9% and CA of 99.3%. A total of 512 isolates were determined to have evaluable results; the EA of evaluable results was 98.0% (Table 3). Clinical and challenge isolate results for *Enterobacteriaceae* determined with OptiRead demonstrated a combined EA of 98.2% and CA of 98.8%. A total of 510 isolates were determined to have evaluable results; the EA of evaluable results was 98.4% (Table 4).

Table 3. *Enterobacteriaceae*, Performance of Clinical and Challenge Isolates, Read Using VIZION

	EA Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Enterobacteriaceae													
Clinical	453	443	97.8	421	412	97.9	453	100.0	0	453	0	0	0
Challenge	108	106	98.1	91	90	98.9	104	96.3	9	96	4	0	0
Total	561	549	97.9	512	502	98.0	557	99.3	9	549	4	0	0

[a] *Enterobacteriaceae* included*: C. freundii, C. koseri, E. coli, E. aerogenes, E. cloacae, K. oxytoca, K. pneumoniae, M. morganii, P. mirabilis, Providencia spp., S. marcescens*

EA – Essential Agreement (+/- 1 dilution)
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Table 4. *Enterobacteriaceae*, Performance of Clinical and Challenge Isolates, Read Using OptiRead

	EA Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Enterobacteriaceae													
Clinical	453	445	98.2	419	412	98.3	453	100.0	0	453	0	0	0
Challenge	108	106	98.1	91	90	98.9	101	93.5	11	93	7	0	0
Total	561	551	98.2	510	509	98.4	554	98.8	11	546	7	0	0

A total of nine resistant strains of *Enterobacteriaceae* were evaluated. No resistant strains of the following species were evaluated: *C. freundii*, *C. koseri*, *E. aerogenes*, *K. oxytoca*, *M. morganii*, *P. mirabilis*, *Providencia* spp. and *S. marcescens*. The sponsor included the following limitation in the device labeling:

> *The ability of the Sensititre system to detect resistance to meropenem/vaborbactam in the following species is unknown because resistant strains were not available at the time of comparative testing: Enterobacter*

cloacae, Proteus mirabilis, Klebsiella oxytoca, Morganella morganii, Enterobacter aerogenes, Citrobacter koseri, Citrobacter freundii, Providencia spp., Serratia marcescens. Isolates yielding meropenem/vaborbactam MIC results suggestive of a resistant interpretive category (≥16/8 µg/mL) should be submitted to a reference laboratory for further testing.

MIC Trending

An analysis of trending was conducted using the combined clinical and challenge data for members of the *Enterobacteriaceae*. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method irrespective of whether the device MIC values are on-scale or not.

The data for *Enterobacteriaceae* results determined to be evaluable for trending analysis is shown in Table 5.

Table 5. Trending in *Enterobacteriaceae*, Clinical and Challenge Isolates

Read Method	Difference in MIC as Compared to the CLSI Reference Method			
	No. Results Evaluable for Trending Analysis	**No. (%) Results ≥1 Dilution Lower**	**No. (%) Results Exact**	**No. (%) Results ≥1 Dilution Higher**
Manual Read	542	179 (33.0)	264 (48.7)	99 (18.3)
Auto Read	543	196 (36.1)	259 (47.7)	88 (16.2)

A trend towards lower MIC readings was observed in the overall performance of *Enterobacteriaceae* compared to the CLSI broth microdilution method which raises concerns for the potential of very major errors. The sponsor included the following footnote to the performance table to address the trending observed for meropenem/vaborbactam.

Meropenem/Vaborbactam MIC values tended to be in exact agreement or at least one doubling dilution lower when testing Enterobacteriaceae compared to the reference broth microdilution method.

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:

Table 6. Breakpoints and Interpretive Categories for Meropenem/Vaborbactam (FDA Drug Label)

Organism	FDA Interpretive Criteria for Meropenem/Vaborbactam MIC (µg/mL)		
	S	I	R
Enterobacteriaceae	≤ 4/8	8/8	≥ 16/8

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.