Food and Drug Administration
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www.fda.gov

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K192250

B Applicant

ThermoFisher Scientific

C Proprietary and Established Names

Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Imipenem-Relebactam in the dilution range of 0.03/4-256/4 µg/mL

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence decision for Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Imipenem-Relebactam in the dilution range of 0.03/4 - 256/4 µg/mL for susceptibility testing of gram-negative microorganisms

B Measurand:

Imipenem-Relebactam 0.03/4-256/4 µg/mL. The relebactam concentration is fixed at 4 µg/mL.

C Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST), growth-based detection

III Intended Use/Indications for Use:

A 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 haemolytic Streptococci other than *S. pneumoniae*. See Indications for Use below.

B 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 Imipenem-relebactam in the dilution range of 0.03/4 - 256/4 ug/mL for testing non-fastidious gram-negative organisms on the Sensititre 18 - 24 hour MIC panel.

Imipenem-relebactam has been shown to be active both clinically and in vitro against the following organisms according to the FDA drug label:

Gram-negative bacteria
Citrobacter freundii
Klebsiella (Enterobacter) aerogenes
Escherichia coli
Enterobacter cloacae
Klebsiella oxytoca
Klebsiella pneumoniae
Pseudomonas aeruginosa

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Due to the occurrence of very major errors with all read methods, isolates of *P. aeruginosa* that provide MICs of 2/4 µg/mL for imipenem/relebactam should be retested using an alternative/method.

Studies of imipenem/relebactam with gram-negative organisms were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing imipenem/relebactam has not been evaluated.

The testing of imipenem/relebactam with gram-negative organisms was performed using the autoreader (OptiRead) and VIZION reading method only. The use of an alternative reading method when testing imipenem/relebactam has not been evaluated.

The ability of the Sensititre system to detect resistance to imipenem-relebactam in the following species is unknown because an insufficient number of resistant strains were available at the time of comparative testing: *Citrobacter freundii*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Escherichia coli*. Isolates yielding imipenem/relebactam MIC results

suggestive of a resistant interpretive category should be submitted to a reference laboratory for further testing.

D Special Instrument Requirements:
Sensititre AIM for device inoculation
Sensititre VIZION or OptiRead for plate reading

IV Device/System Characteristics:

A 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.

B Principle of Operation:

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System includes multi-well plastic microtiter plates that contain doubled dilutions of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read by the digital device, 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 visually determine MIC results. The Sensititre OptiRead utilizes fluorescence technology to read the microbroth dilution plates after 18 to 24 hours of 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):
The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftazidime/Avibactam in the dilutions range of 0.015/4 - 32/4 ug/mL

B Predicate 510(k) Number(s):
K152774

C Comparison with Predicate(s):

Table 1. Comparison with the Predicate

Device & Predicate Device(s):	**K192250 Imipenem/ Relebactam**	**K152774 Ceftazidime/ Avibactam**
Device Trade Name	Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Imipenem-Relebactam in the dilution range of 0.03/4 – 256/4 µg/mL	Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftazidime-Avibactam in the dilution range of 0.015/4 – 32/4 µg/mL
General Device Characteristic Similarities		
Intended Use/Indications 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 comprising of *Enterobacteriaceae*, *Pseudomonas aeruginosa,* and other non-*Enterobacteriaceae* and of non-fastidious Gram positive isolates, comprising of *Staphylococcus* sp., *Enterococcus* sp., and Beta haemolytic streptococci other than *S. pneumoniae.*	Same
Test Panel	Each 96 well plate is precision dosed with selected antimicrobial agents and substrates for the fluorescent reads, then dried. The bacterial suspension in the appropriate broth is used	Same

Device & Predicate Device(s):	K192250 Imipenem/ Relebactam	K152774 Ceftazidime/ Avibactam
	to rehydrate the plate.	
Test Organisms	Non-fastidious Gram-negative isolates	Same
Incubation	18-24 hours	Same
General Device Characteristic Differences		
Reading method	1) Automatically - with the AutoReader/OptiRead (fluorogenic substrate technology) 2) On the VIZION - Digital Viewing Device	Same, plus manually - using a manual viewer via visual interpretation of growth
Antibiotic	Imipenem/Relebactam 0.03/4 – 256/4 µg/mL	Ceftazidime/Avibactam 0.015/4 – 32/4 µg/mL

VI Standards/Guidance Documents Referenced:

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

CLSI M100-S028: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Eighth Informational Supplement

CLSI M7-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   A reproducibility study was performed at four sites using a panel comprised of 13 strains of indicated non-fastidious Gram-negative bacteria including: *E. coli* (five isolates), *E. cloacae* (one isolate), *K. oxytoca* (two isolates), *K. pneumoniae* (four isolates) and *P. aeruginosa* (one isolate). All isolates were tested in triplicate over three days with each read method (i.e., VZION and OptiRead). The Sensititre Aim inoculator was used for plate inoculation. The mode MIC was determined and the reproducibility was calculated based on the MIC values falling within ± 1 dilution of the mode MIC value. Reproducibility was greater than 95% for both read methods and was acceptable.

2. Linearity:

   Not Applicable

3. Analytical Specificity/Interference:

Not Applicable

4. Assay Reportable Range:

Not Applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Quality Control Testing. Quality control strains recommended by the CLSI were tested with Imipenem/Relebactam at four sites. The QC organisms tested were *K. pneumoniae* ATCC BAA 1705 and *K. pneumoniae* ATCC BAA-2814. The QC strains were tested a minimum of 20 times per site and read using the VIZION and OptiRead. The results demonstrate that the Sensititre 18-24 hour MIC Breakpoint panel with imipenem/relebactam produced quality control results in the recommended range > 95% of the time (Table 2).

Imipenem was tested 20 times per site with *K. pneumoniae* ATCC BAA-1705 to confirm the integrity of the QC strain; all results demonstrated the integrity of the strain. The sponsor included the following statement in the device labeling as a footnote to the QC table:

> *Imipenem should be included in the quality control of imipenem-relebactam as an integrity check with testing K. pneumoniae ATCC BAA 1705.*

Table 2. Quality Control Results for Sensititre 18 - 24 hour MIC or Breakpoint Susceptibility System with Imipenem/Relebactam with the VIZION and OptiRead Methods.

QC Organism	Imipenem/ Relebactam Range (µg/mL)	Concentration (µg/mL)	Reference Method	Sensititre	
				Read method	
				VIZION	OptiRead
K. pneumoniae ATCC BAA-1705	0.03/4 – 0.25/4 µg/mL	0.015	0	0	0
		0.03	2	0	0
		0.06	70	11	32
		0.12	6	66	44
		0.25	1	3	4
		0.5	1	0	0
K. pneumoniae ATCC BAA-2814	0.06/4 – 0.25 µg/mL	0.03	1	0	0
		0.06	35	1	2
		0.12	41	54	70
		0.25	3	25	8
		0.5	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 panel inoculation. Only results from pure cultures were evaluated.

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

6. Detection Limit:

   Not Applicable

7. Assay Cut-Off:

   Not Applicable

8. Accuracy (Instrument):

   Not Applicable

9. Carry-Over:

   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
   Results obtained with Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Imipenem/Relebactam were compared to results obtained with the CLSI broth microdilution reference panel. Drug dilutions were prepared as indicated in CLSI M100, 28th ed. During 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. The sponsor added the following limitations to the device labeling to reflect the inoculation and read methods:

   Studies of imipenem/relebactam with Gram-negative organisms were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing imipenem/relebactam has not been evaluated.

   The testing of imipenem/relebactam with Gram-negative organisms was performed using the autoreader (OptiRead) and VIZION reading method only. The use of an alternative reading method when testing imipenem/relebactam has not been evaluated.

   Clinical testing was performed at four sites, three of which were in the United States; one site was an internal site. A total of 312 *Enterobacteriaceae* were tested comprised of the following species: *Citrobacter freundii* (20 isolates), *Enterobacter cloacae* (41 isolates), *Escherichia coli* (104 isolates), *Klebsiella aerogenes* (20 isolates), *Klebsiella oxytoca* (43 isolates), *K. pneumoniae* (84 isolates). Testing was also performed with *Pseudomonas aeruginosa* (40 isolates). All the clinical isolates tested were fresh isolates.

A total of 104 challenge isolates were tested at a single internal site. Species tested included: *C. freundii* (5 isolates), *E. cloacae* (5 isolates), *E. coli* (13 isolates), *K. aerogenes* (7 isolates), *K. oxytoca* (5 isolates), *K. pneumoniae* (27 isolates) and *P. aeruginosa* (42 isolates).

Results were evaluated for essential agreement (EA) and category agreement (CA). For CA evaluation, breakpoints used were those noted on the FDA-Recognized Susceptibility Test Interpretive Criteria Website (STIC) (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm).

The results from testing clinical and challenge *Enterobacteriaceae* isolates with the VIZION demonstrated a combined EA of 97.3% and CA of 98.4%. A total of 358/374 isolates provided evaluable results; the EA of evaluable results was 97.2% (Table 3). The results from testing clinical and challenge *Enterobacteriaceae* isolates with the OptiRead demonstrated a combined EA of 95.7% and CA of 98.7%. A total of 359/374 isolates showed evaluable results; the EA of evaluable results was 95.5% (Table 4).

For clinical and challenge testing with *P. aeruginosa*, results obtained with the VIZION demonstrated a combined EA of 97.6% and CA of 92.7%. A total of 76/82 isolates provided evaluable results; the EA of evaluable results was 97.4% (Table 3). Testing of *P. aeruginosa* with the OptiRead demonstrated a combined EA of 98.8% and CA of 93.9%. A total of 78/82 isolates provided evaluable results; the EA of evaluable results was 98.7% (Table 4).

Table 3. Performance for Clinical and Challenge Isolates Read Using VIZION

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Enterobacteriaceae [a] **(Breakpoints ≤1/4, 2/4, ≥4/4 µg/mL)**													
Clinical	312	304	97.4	298	290	97.3	311	99.7	0	312	1	0	0
Challenge	62	60	96.8	60	58	96.7	57	91.9	15	43	4	1	0
Total	374	364	97.3	358	348	97.2	368	98.4	15	355	5	1	0
P. aeruginosa **(Breakpoints ≤ 2/4, 4/4, ≥8/4 µg/mL)**													
Clinical	40	40	100.0	40	40	100.0	35	87.5	1	36	5	0	0
Challenge	42	40	95.2	38	36	94.7	41	97.6	18	23	0	0	1
Total	82	80	97.6	78	76	97.4	76	92.7	19	59	5	0	1

[a] Includes *C. freundii, E. cloacae, E. coli, K. aerogenes, K. oxytoca, K. pneumoniae*

Table 4. Performance for Clinical and Challenge Isolates Read Using OptiRead

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Enterobacteriaceae [a] **(Breakpoints ≤1/4, 2/4, ≥4/4 µg/mL)**													
Clinical	312	298	95.5	299	285	95.3	311	99.7	0	312	1	0	0
Challenge	62	60	96.8	60	58	96.7	58	93.5	15	43	3	1	0
Total	374	358	95.7	359	343	95.5	369	98.7	15	355	4	1	0
P. aeruginosa **(Breakpoints ≤ 2/4, 4/4, ≥8/4 µg/mL)**													
Clinical	40	40	100.0	40	40	100.0	36	90.0	1	36	4	0	0
Challenge	42	41	97.6	38	37	97.4	41	97.6	18	23	0	0	1
Total	82	81	98.8	78	77	98.7	77	93.9	19	59	4	0	1

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.

With both the VIZION and OptiRead, one isolate of *P. aeruginosa* provided a very major error for a very major error rate of 5.3%. The sponsor included the following limitation in the device labeling.

> *Due to the occurrence of very major errors with all read methods, isolates of P. aeruginosa that provide MICs of 2/4 µg/mL for imipenem/relebactam should be retested using an alternative/method.*

An insufficient number of resistant organisms were encountered during the clinical evaluation for the following species: *C. freundii, E. cloacae, E. coli, K. aerogenes* and *K. oxytoca*. The sponsor added the following limitation to the device labeling:

> *The ability of the Sensititre system to detect resistance to imipenem-relebactam in the following species is unknown because an insufficient number of resistant strains were available at the time of comparative testing: Citrobacter freundii, Klebsiella oxytoca, Enterobacter cloacae, Klebsiella aerogenes, and Escherichia coli. Isolates yielding imipenem/relebactam MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory for further testing.*

To address the testing and reporting of non-indicated species the following comment was added to the Precautions section of the device labeling:

> *Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labelling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

Resistance Mechanisms
Challenge isolates of *Enterobacteriaceae* and *P. aeruginosa* harboring various molecular mechanisms of resistance noted in the FDA drug label were evaluated with Sensititre 18 - 24 hour MIC or Breakpoint Susceptibility System with Imipenem/Relebactam. The following drug label- listed resistance mechanisms were evaluated: *KPC, CTX-M, SHV, TEM, CMY, ACT/MIR*.

MIC Trending
An analysis of trending was calculated using the combined clinical and challenge data for each organism group. 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. Trending results are shown in Table 5. Results for *Enterobacteriaceae* were stratified by species to determine if particular trends were observed. The acceptable percent difference between higher and lower dilution readings is <30%.

Table 5. Trending for Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Imipenem/Relebactam

Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
VIZION	*C. freundii*	22	1 (4.6)	6 (27.3)	15 (68.2)	63.6	Yes
	E. cloacae	46	5 (10.9)	14 (30.4)	27 (58.7)	47.8	Yes
	E. coli	112	4 (3.6)	35 (31.3)	73 (65.2)	61.6	Yes
	K. aerogenes	26	0	7 (26.9)	19 (73.1)	73.1	Yes
	K. oxytoca	47	0	16 (34.0)	31 (66.0)	66.0	Yes
	K. pneumoniae	107	12 (11.2)	30 (28.0)	65 (60.8)	49.5	Yes
	P. aeruginosa	82	4 (4.9)	46 (56.1)	32 (39.0)	34.2	Yes
OptiRead	*C. freundii*	23	1 (4.4)	5 (21.7)	17 (73.9)	69.6	Yes
	E. cloacae	44	1 (2.3)	16 (36.4)	27 (61.4)	59.1	Yes
	E. coli	113	6 (5.3)	35 (31.0)	72 (63.7)	58.4	Yes
	K. aerogenes	27	1 (3.7)	5 (18.5)	21 (77.8)	74.1	Yes
	K. oxytoca	47	1 (2.1)	17 (36.2)	29 (61.7)	59.6	Yes
	K. pneumoniae	106	14 (13.2)	35 (33.0)	57 (53.8)	40.6	Yes
	P. aeruginosa	82	8 (9.8)	46 (56.1)	28 (34.2)	24.4	No

A trend toward higher MIC readings was observed for *Enterobacteriaceae* and *P. aeruginosa* with VIZION and for *Enterobacteriaceae* with OptiRead. The sponsor included the following footnote to the performance table to address the trending observed for imipenem/relebactam:

> *Imipenem-relebactam MIC values tended to be in exact agreement or at least one dilution higher when testing C. freundii, E. cloacae, E. coli, K. aerogenes, K. oxytoca and K. pneumoniae with both the VIZION and OptiRead read methods and when testing P. aeruginosa with the VIZION read method compared to the CLSI reference broth microdilution method.*

2. Matrix Comparison:

   Not Applicable

C Clinical Studies:

1. Clinical Sensitivity:

   Not Applicable

2. Clinical Specificity:

   Not Applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not Applicable

D Clinical Cut-Off:

Not Applicable

E Expected Values/Reference Range:

Table 6. FDA-Identified Interpretive Criteria for Imipenem/Relebactam

Organism	FDA Interpretive Criteria for Imipenem/Relebactam MIC (µg/mL)[a]		
	S	I	R
Enterobacteriaceae[b]	≤ 1/4	2/4	≥ 4/4
P. aeruginosa	≤ 2/4	4/4	≥ 8/4

[a] FDA STIC Webpage
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm
[b] *C. freundii, E. cloacae, E. coli, K. aerogenes, K. oxytoca, K. pneumoniae*

VIII Proposed Labeling:

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

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e. breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. The protocol outline the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate ETEST Imipenem/Relebactam (IPR) (0.002/4 – 32/4) when revised breakpoints for imipenem/relebactam are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, bioMérieux will update the imipenem/relebactam device label to include (1) the new breakpoint, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.