510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K231994

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Sulbactam-durlobactam in the dilution range of 0.015/4-32/4 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 determination for the addition of sulbactam-durlobactam at concentration of 0.015/4-32/4 µg/mL to the Sensititre 18-24 hour MIC or Breakpoint Susceptibility System for testing *Acinetobacter baumannii-calcoaceticus* complex isolates.

B Measurand:

Sulbactam-durlobactam in the dilution range of 0.015/4-32/4 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* spp., *Enterococcus* spp., and beta-haemolytic streptococci other than *S. pneumoniae*.

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 sulbactam-durlobactam in 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.

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

Acinetobacter baumannii-calcoaceticus complex

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Limitations

Studies of sulbactam-durlobactam with *Acinetobacter baumannii-calcoaceticus* complex were performed using the AIM autoinoculator inoculation method and OptiRead/ARIS and Vizion reading methods only. The use of alternative inoculation methods or alternative reading methods when testing sulbactam-durlobactam have not been evaluated.

D Special Instrument Requirements:

Sensititre AIM for device inoculation
Sensititre Vizion or OptiRead/ARIS for plate reading

IV Device/System Characteristics:

A Device Description:

The Sensititre MIC and Breakpoint Susceptibility panel is a multi-well microtiter plate, dosed with dried, stabilized antimicrobial agents at appropriate concentrations. It is a micro-version of the classic broth dilution method which can provide both qualitative and quantitative susceptibility results. A standardized organism suspension is prepared in cation adjusted Mueller-Hinton broth with TES buffer. After inoculation, plates are sealed with an adhesive seal, incubated at 34-36°C for 20-24 hours and examined for bacterial growth. Antimicrobial

susceptibility test results can be read by using a digital reader (Vizion) or an automated reader (OptiRead/ARIS).

B Principle of Operation:

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System includes multi-well microtiter plates that contain doubled dilution of antimicrobial agents. Results can be read by a digital reading device (Vizion) or by the use of an automated reader (OptiRead/ARIS).

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 OptiRead utilizes fluorescence technology for 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 fluorogenic substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The plates are prepared with substrate already added to the plate. Enzymatic action of the bacterial surface enzymes on the specific substrates cleaves this bond releasing the fluorophore which is now capable of fluorescing. The amount of fluorescence detected is directly related to the activity of bacterial surface enzymes and therefore, to the bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Cefiderocol in the dilution range of 0.03-64 µg/ml

B Predicate 510(k) Number(s):

K203741

C Comparison with Predicate(s):

Table 1. Comparison with the Predicate Device

Device & Predicate Device(s):	**Device K231994**	**Predicate K203741**
Device Trade Name	Sensititre 18-24 hour Susceptibility System with Sulbactam-durlobactam in the dilution range of 0.015/4-32/4-µg/ml	Sensititre 18-24 hour Susceptibility System with Cefiderocol in the dilution range of 0.03-64µg/ml
General Device Characteristic Similarities		

Device & Predicate Device(s):	Device K231994	Predicate K203741
Intended Use/Indications For Use	The Sensititre MIC or Breakpoint Susceptibility system is an *in vitro* diagnostic product for clinical susceptibility testing.	Same
Test Panel	Each 96 well plate is precision dosed with selected antimicrobial agents and substrate for the fluorescent reads, then dried. The bacterial suspension in the appropriate broth is used to rehydrate the plate.	Same
Reading Method	Detection of growth or detection of fluorescence	Same
Instrument	Automated on an ARIS/Autoreader/ OptiRead using fluorescence or on the Vizion by visual reading of growth.	Same
General Device Characteristic Differences		
Antibiotic and Dilution Range	Sulbactam-durlobactam 0.015/4-32/4µg/ml	Cefiderocol 0.03-64µg/ml
Incubation Time	20-24 hours	Enterobacterales 18-24 hours *Acinetobacter baumannii* 20-24 hours
Test Organisms	*Acinetobacter baumannii-calcoaceticus* complex	*Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens* and *Acinetobacter baumannii*

VI Standards/Guidance Documents Referenced:

Guidance for Industry and FDA - Class II Special Controls Guidance Document:

Antimicrobial Susceptibility Test (AST) Systems – August, 2009.

CLSI M07-ED11: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – January, 2018.

CLSI M100-ED32: Performance Standards for Antimicrobial Susceptibility Testing – February, 2022.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   A reproducibility study was performed at four sites using a panel of ten isolates of *A. baumannii-calcoaceticus* complex for a total of 360 data points read each using the Vizion digital reader and OptiRead/ARIS (auto read). Plates were inoculated with the AIM autoinoculator after preparation of a standard suspension. The mode MIC was determined, and the reproducibility was calculated based on the MIC values falling withing ±1 doubling dilution of the mode MIC value. Reproducibility was 100% for best case scenario using both read methods and 97.8% (Vizion) and 99.4% (OptiRead/ARIS) for worst case scenario which was considered to be 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):
   The quality control (QC) strain recommended by CLSI, *A. baumannii* NCTC 13304, was tested with sulbactam-durlobactam at four sites. The QC strain was tested a minimum of 20 times per site and read using the Vizion digital reader and OptiRead/ARIS (auto read). The QC strain was also tested with the reference method.

   The results demonstrate that the Sensititre 18-24 hour MIC or Breakpoint panel with sulbactam-durlobactam produced quality control results for *A. baumannii* NCTC 13304 in the recommended range >95% of the time (Table 2). Quality control results for *A. baumannii* NCTC 13304 were not in the recommended range 95% of the time with the reference method (88/93, 94.6% within range). However, these data were considered acceptable since all quality control results were back in-range after the replacement of the QC strain stock solution with a fresh stock solution, per CLSI guideline. Thus, the quality control results are considered acceptable.

Table 2. Quality Control Results for Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Sulbactam-durlobactam with the Vizion and OptiRead/ARIS Methods

QC Organism	Sulbactam-durlobactam Range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre	
				Read method	
				Vizion	OptiRead/ARIS
A. baumannii NCTC 13304[a]	0.5/4-2/4	0.24/4	5	0	0
		0.5/4	20	13	53
		1/4	60	80	39
		2/4	8	3	4
		4/4	0	0	0

[a] *A. baumannii* NCTC 13304 in-range QC results: Reference, 94.6%; Vizion, 100%; OptiRead/ARIS, 100%

Inoculum Density: Inoculum density checks were performend for all QC, reproducibility and clinical isolates tested.

Purity Checks: Purity checks were performed each day for each clinical, challenge, reproducibility and QC strain tested. Only results from pure cultures were evaluated.

Growth Failures: There were no growth failures in the Sensititre panels.

6. Detection Limit:
   Not Applicable

7. Assay Cut-Off:
   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
   Testing of the Sensititre 18-24 hour MIC or Breakpoint panel with sulbactam-durlobactam was performed at three external sites and one internal site. Results were compared to results obtained with the CLSI broth microdilution reference panel. Sensititre panels were inoculated using AIM autoinoculator and results were interpreted using both the Vizion digital reader and the ARIS/OptiRead (auto read). Reference panels were inoculated according to recommendations in the M07 CLSI document and results were interpreted using a mirrored reader. No inoculation system other than the AIM autoinoculator and no reading method other than ARIS/OptiRead and Vizion were used in the comparative study. To address the inoculation and reading methods for the Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with sulbactam-durlobactam, the sponsor included the following limitation in the device labeling:

   Studies of sulbactam-durlobactam with Acinetobacter baumannii-calcoaceticus complex were performed using the AIM autoinoculator inoculation method and ARIS/OptiRead and Vizion reading methods only. The use of alternative inoculation methods or alternative reading methods when testing sulbactam-durlobactam have not been evaluated.

The testing conditions for the Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with sulbactam-durlobactam consisted of the following:

- **Media**: cation adjusted Mueller-Hinton broth with TES buffer (CAMHBT)
- **Inoculum**: A standardized suspension (0.5 McFarland) suspension was prepared from a fresh primary agar plate in sterile water. Ten µL of the standardized suspension was transferred to 11 mL tube of cation adjusted Mueller Hinton broth with TES buffer. Fifty µL of the broth suspension was inoculated into the panel wells using the AIM autoinoculator.
- **Incubation**: At 35 ± 1°C in a non-CO_2 incubator for 20-24 hours

A total of 231 *Acinetobacter baumannii-calcoaceticus* complex clinical isolates and 56 *Acinetobacter baumannii-calcoaceticus* complex challenge isolates were evaluated. For *Acinetobacter baumannii-calcoaceticus* complex read using Vizion, the combined clinical and challenge results (286 isolates) were acceptable at 96.5% and 96.9% for EA and CA, respectively, with 8 minor errors and 1 major error (1/266 = 0.4%) (Table 3).

Table 3. Sulbactam-durlobactam Results for *Acinetobacter baumannii-calcoaceticus* complex with Vizion

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	major	vmj
Acinetobacter baumannii-calcoaceticus complex (≤4/4, 8/4, ≥16/4 µg/mL)													
Clinical	230	224	97.4	227	221	97.4	224	97.4	7	222	5	1	0
Challenge	56	52	92.9	52	48	92.3	53	94.6	8	44	3	0	0
Combined	286	276	96.5	279	269	96.4	277	96.9	15	266	8	1	0

EA – Essential Agreement (±1 doubling dilution) **min** – minor discrepancies
CA – Category Agreement **maj** – major discrepancies
EVAL – Evaluable isolates **vmj** – very major discrepancies
R – Resistant isolates

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 or results in which an off-scale result is at least two doubling dilutions from the on scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

For *Acinetobacter baumannii-calcoaceticus* complex read using ARIS/OptiRead, the combined clinical and challenge performance results (287 isolates) were acceptable at 95.5% and 97.2% for EA and CA, respectively, with 6 minor errors and 2 major error (2/267 = 0.8%) (Table 4).

Table 4. Sulbactam-durlobactam Results for *Acinetobacter baumannii-calcoaceticus* complex with ARIS/OptiRead

	Tot	No.EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	major	vmj
Acinetobacter baumannii-calcoaceticus complex (≤4/4, 8/4, ≥16/4 µg/mL)													
Clinical	231	220	95.2	229	218	95.2	226	97.8	7	223	3	2	0
Challenge	56	54	96.4	52	50	96.2	53	94.6	8	44	3	0	0
Combined	287	274	95.5	281	268	95.4	279	97.2	15	267	6	2	0

Resistance Mechanisms

Challenge isolates of *Acinetobacter baumannii-calcoaceticus* complex 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 sulbactam-durlobactam. The *Acinetobacter baumannii-calcoaceticus* complex isolates expressing serine betalactamases included in Ambler Class A (CTX-M-, TEM-, PER- and SHV-type), Class C (ADC-type), and broad-spectrum activity against Class D (OXA-type) enzymes were evaluated.

MIC Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained for both Vizion and ARIS/OptiRead read methods for *Acinetobacter baumannii-calcoaceticus* complex. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Species for which the difference between the percentage of isolates with higher vs. lower readings was > 30% and for which the confidence interval was determined to be statistically significant were considered to show evidence of trending. No trending was observed for *Acinetobacter baumannii-calcoaceticus* complex and sulbactam-durlobactam using Vizion and ARIS/OptiRead (Table 5).

Table 5. Trending Observed by Vizion and ARIS/OptiRead Read Method for *Acinetobacter baumannii-calcoaceticus* complex with Sulbactam-durlobactam

Organism/Read Method	Total Evaluable for Trending	>= 1 Dilution lower No. (%)	Exact No. (%)	>= 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
A. baumannii-calcoaceticus complex / Vizion Read	282	54, (19.15)	172	56, (19.86)	1% , (-6%, 7%)	No
A. baumannii-calcoaceticus complex / ARIS/OptiRead Read	284	42, (14.79)	168	74, (26.06)	11% , (5%, 18%)	No

Testing/Reporting MIC for Non-indicated Species:

For this review, the interpretive criteria are applied to the organisms/organism groups according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and Cosmetic Act, the following statement is added to the Precautions section of the device labeling to address testing and reporting of non-indicated species:

> *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.*

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 Sulbactam-Durlobactam

Organism	Interpretive Criteria for Sulbactam-durlobactam[a]		
	Susceptible	Intermediate	Resistant
Acinetobacter baumannii-calcoaceticus complex	≤4/4	8/4	≥16/4

[a] FDA STIC Webpage

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/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that ThermoFisher intends to use to evaluate the Sensititre 18–24-hour MIC or Breakpoint Susceptibility System with Sulbactam-durlobactam in the dilution range of 0.015/4 – 32/4 µg/mL when revised breakpoints for sulbactam-durlobactam are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, ThermoFisher will update the sulbactam-durlobactam device label to include (1) the new breakpoints, (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.