510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193508

B Applicant

Oxoid Limited (Part of Thermo Fisher Scientific)

C Proprietary and Established Names

Thermo Scientific Oxoid Eravacycline Disc (20ug) ERV20

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JTN	Class II	21 CFR 866.1620 - Antimicrobial Susceptibility Test Disc	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain substantial equivalence determination for Eravacycline Antimicrobial Test Disk

B Measurand:

Eravacycline (20 µg) ERV20

C Type of Test:

Antimicrobial Test Disc

III Intended Use/Indications for Use:

A Intended Use(s):

Thermo Scientific Oxoid Antimicrobial Susceptibility Test (AST) Discs are used in the semi-quantitative agar diffusion test method for *in vitro* susceptibility testing.

B Indication(s) for Use:

Thermo Scientific Oxoid Antimicrobial Susceptibility Test (AST) Discs are used in the semi-quantitative agar diffusion test method for *in vitro* susceptibility testing.

Thermo Scientific Oxoid Eravacycline Disc (20µg) ERV20 can be used to determine susceptibility to Eravacycline against the following bacteria for which Eravacycline has been shown to be active both clinically and *in vitro*:

Gram-negative bacteria:
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae

In vitro data are available for the following microorganisms, but clinical significance is unknown:

Gram-negative bacteria:
Citrobacter koseri
Klebsiella aerogenes

C Special Conditions for Use Statement(s):

- Rx - For Prescription Use Only

- The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than "Susceptible" should be submitted to a reference laboratory for further testing.

D Special Instrument Requirements:

Not applicable

IV Device/System Characteristics:

A Device Description:

Thermo Scientific Oxoid Eravacycline Disc (20 µg) ERV20 comprise 6 mm disks prepared by impregnating high absorbent paper with accurately determined amounts of eravacycline. The disk is clearly marked on both sides with the code ERV20. The code designates the agent (eravacycline) and the drug content (20 µg).

Thermo Scientific Oxoid disks are supplied in cartridges containing 50 disks each; there are 5 cartridges per pack. Each cartridge is individually sealed together with a desiccant capsule in a

foil covered see-through blister pack. Thermo Scientific Oxoid disks can be dispensed using a Thermo Scientific Oxoid Disk Dispenser.

B Principle of Operation:

A suitable therapeutic agent can be determined using filter paper disks impregnated with specified concentrations of antimicrobial agents placed on the surface of a suitable test medium. The test is performed by inoculating pure cultures of clinical isolates onto the test medium and placing the AST disk on the surface of the medium. The antibiotic within the disk diffuses into the agar. After incubation, the zones of inhibition around the disks are measured and compared against recognized zone diameter ranges for the specific antimicrobial agent/organism combinations being tested.

V Substantial Equivalence Information:

A Predicate Device Name(s):

HardyDisk AST Eravacycline 20µg (ERV20)

B Predicate 510(k) Number(s):

K182357

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device K193508**	**Predicate K182357**
Device Trade Name	Thermo Scientific Oxoid Eravacycline Disc (20 µg) ERV20	HardyDisk Eravacycline Disk 20 µg (ERV20)
General Device Characteristic Similarities		
Test Method	Antimicrobial susceptibility testing using paper disks impregnated with an antimicrobial agent	Same
Antimicrobial Agent	Eravacycline	Same
Antimicrobial Agent Concentration	20 µg	Same
Reading Method	The user will interpret the zone diameter according to the established interpretive criteria for the drug	Sam
General Device Characteristic Differences		
Manufacturing Specifications	Oxoid's specifications	Hardy Diagnostics' specifications

VI Standards/Guidance Documents Referenced:

- CLSI M02-13th ed., "Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard"; January 2018

- CLSI M100-S29, Performance Standards for Antimicrobial Susceptibility Testing; Twenty-ninth Informational Supplement

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility was conducted at an external site using 18 indicated organisms, tested with two disk lots on three separate days. Each test was visually read by three independent readers with results blinded, resulting in 324 data points for evaluation.

   The reproducibility study included the following: 2 *Citrobacter freundii*, 2 *Citrobacter koseri*, 5 *Enterobacter cloacae*, 3 *Escherichia coli*, 1 *Klebsiella aerogenes*, 1 *Klebsiella oxytoca* and 4 *Klebsiella pneumoniae* isolates. Reproducibility was assessed by considering a ±3 mm difference in zone diameter comparing test results with the modal zone diameter value. All results were ≤2 mm of the mode results. Results are shown in **Table 1** below.

Table 1: Reproducibility Summary

Between Disk Lots			Across Readers			
Lot #1	**Lot #2**	**All Lots**	**Reader 1**	**Reader #2**	**Reader #3**	**All Readers**
100% (162/162)	100% (162/162)	100% (324/324)	100% (108/108)	100% (108/108)	100% (108/108)	100% (324/324)

   The reproducibility across manual readers and disk lots is >95% and meets the acceptance criteria.

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 (QC) Testing:
The CLSI-recommended quality control (QC) isolate, *Escherichia coli* ATCC 25922, was tested a sufficient number of times (i.e., 20 replicates per lot per reader), including each day susceptibility testing of isolates was performed. One predicate disk lot and two Oxoid disk lots were used. Each test was visually read by three independent readers, resulting in 120 Oxoid disk data points and 60 predicate disk data points. The performance is shown in **Table 2** below.

Table 2: Quality Control Performance

	Zone Diameter in millimeters (mm)		
QC Organism	**Range**	**Predicate[1]**	**Oxoid[2]**
E. coli ATCC 25922 Expected Range: 16 – 23 mm	15		
	16		
	17		
	18	6	
	19	1	8
	20	18	51
	21	16	29
	22	10	19
	23	9	13
	24		

[1] One predicate disk lot
[2] Two Oxoid disk lots

The Oxoid disk QC performance is >95% (100%, 120/120 within the expected range) and was considered acceptable.

Inoculum Density Check:
Colony counts were conducted for all QC and reproducibility isolates, as well as 10% of clinical isolates. All were within the expected range.

6. Detection Limit:

Not applicable

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

The Oxoid disk was compared with an FDA-cleared disk of the same antimicrobial, mass/concentration, and content. The study was conducted at one testing site. Three independent operators participated in reading of test results with isolates evenly distributed to mimic testing at multiple sites. The study included 300 clinical isolates recovered during the 2017 eravacycline surveillance testing of the drug development clinical trial. The isolates were selected to give a similar MIC distribution to the whole population (within each species

and eravacycline MIC). An additional 75 challenge isolates were also evaluated. These isolates included 56 isolates from the 2017 eravacycline surveillance (chosen to have a similar MIC distribution to the whole population with a selection bias to enrich for non-susceptible isolates) that were whole-genome-sequenced and 19 isolates with known resistance mechanisms provided by the drug manufacturer.

The following species were evaluated as clinical isolates in the study: *Citrobacter freundii* (29), *Citrobacter koseri* (24), *Enterobacter cloacae* (45), *Escherichia coli* (55), *Klebsiella aerogenes* (47), *Klebsiella oxytoca* (49) and *Klebsiella pneumoniae* (51). The following species were evaluated as challenge isolates in the study: *Citrobacter freundii* (7), *Citrobacter koseri* (5), *Enterobacter cloacae* (13), *Escherichia coli* (7), *Klebsiella aerogenes* (10), *Klebsiella oxytoca* (8) and *Klebsiella pneumoniae* (25). The performance of the Oxoid disk for *Enterobacteriaceae* when compared to an FDA-cleared disk is shown in **Table 3**.

Table 3: Performance of Oxoid Eravacycline with *Enterobacteriaceae*

	Total	**CA N**	**CA %**	**# S**	**#NS**	**MIN**	**MAJ**	**VMJ**
Clinical	300	299	96.7	300	0	n/a	1	0
Challenge	75	71	94.7	46	29	n/a	4	0
Combined	**375**	**370**	**98.7**	**346**	**29**	**n/a**	**5**	**0**

n/a: Not applicable due to the lack of an intermediate breakpoint

CA – Category Agreement
S – Susceptible isolates
NS – Non-susceptible isolates
MIN – minor errors
MAJ – major errors
VMJ – very major errors

The performance of the Oxoid Eravacycline disk as compared to an FDA-cleared disk is acceptable (CA = 98.7%). There were no very major discrepancies and five major discrepancies that were each within a 1 mm disk zone diameter.

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included as a footnote to the performance table in the device labeling to address testing 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 labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

Eravacycline does not have intermediate or resistant interpretive criteria due to the absence of a sufficient number of resistant isolates. The following statement is included in the Limitations section of the device labeling:

The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than "Susceptible" should be submitted to a reference laboratory for further testing.

Resistance Mechanisms in Challenge Isolates:

The seventy-five isolate challenge set included *Enterobacteriaceae* isolates harboring various molecular mechanisms of resistance noted in the FDA drug label, including tetracycline-resistance and β-lactam-resistance markers. Information regarding other resistance mechanisms is addressed in the device labeling with the following footnote:

Activity of eravacycline was demonstrated in vitro against Enterobacteriaceae in the presence of certain beta-lactamases, including extended spectrum β-lactamases, and AmpC. However, some beta-lactamase-producing isolates may confer resistance to eravacycline via other resistance mechanisms. The performance of Oxoid Eravacycline disc (20 μg) ERV20 is unknown for Enterobacteriaceae with other resistance mechanisms.

Secondary Analysis:

A secondary analysis of the results obtained with the 375 clinical and challenge isolates was also performed. The analysis was conducted to assess the qualitative categorical agreement (CA) of the Oxoid Eravacycline disk diffusion results compared to the reference broth microdilution (BMD) results (based on historical data from BMD testing performed at the initial recovery of isolates during the drug clinical trial). Because of the similarities between the Oxoid disk and the comparator disk with respect to content, drug concentration and test methods, a similar analysis was also conducted with the comparator FDA-cleared disk diffusion results compared to the reference BMD results.

Analysis of the Oxoid disk showed a CA of 94.7% with no major errors (MAJ) and 18 very major errors (VMJ) out of 52 non-susceptible isolates (34.6%). In the absence of an intermediate breakpoint, further analysis and adjustment can be performed for categorical errors that are within "essential agreement" ("EA") of the reference MIC. The adjustment is based on the equivalence of one MIC doubling dilution with a 3 mm disk zone diameter at the breakpoint point. After "EA" adjustment, the total VMJ rate is 12/52 (23.1%) for the Oxoid disk. The analysis also revealed similar trends for the comparator disk.

The high number of categorical errors generated with both the Oxoid and comparator disks warranted an investigation into the possible variability of the BMD method since only a single reference MIC value was obtained for each isolate. A testing and analysis plan was developed solely to address the potential variability. It consisted of triplicate BMD testing performed concurrently with single Oxoid disk diffusion testing of all 18 isolates that yielded a discordant result (i.e., VMJ). In addition, a control set representing ~25% of isolates with concordant results (percentage calculated based on the total number of concordant results) were included in the concurrent testing. The control set comprised 68 isolates that had on-scale MIC values and were not in exact agreement with the disk diffusion result. The categorical interpretations of the disk diffusion value and mode/median MIC value were used to determine categorical agreement.

The investigation showed slight variability within the triplicate results of the BMD tests performed on both sets of isolates (i.e., isolates with initial concordant or discordant results); only the occasional one-doubling dilution difference and one instance of a two-doubling dilution difference were observed. However, variability (up to six doubling dilutions in some instances) was observed with both sets of isolates when comparing the historical MIC value (used in the above secondary analysis) with the final MIC value obtained after triplicate and concurrent testing with the disk diffusion method. When evaluating the concurrently obtained MIC and disk diffusion results, all isolates of the control set yielded concordant results based on categorical agreement. This result supported proceeding with analysis of the rest of the data obtained from this investigation. When evaluating the 18 isolates with initial discordant results, 13 isolates yielded concordant results. Four of the remaining five discordant results (i.e., VMJ), were in "EA" and, as noted above, an adjustment of the error rate was made due to the lack of an intermediate breakpoint. The single unresolved VMJ error (from *Klebsiella oxytoca*) is addressed in the following footnote to the performance table in the device labeling:

> *Of the three non-susceptible Klebsiella oxytoca strains tested, one resulted in a potential very major error with the eravacycline disc when compared to the broth microdilution result.*

Due to the observed variability with the historical and recent MIC data as well as the resolution of most of the VMJ errors provided by the investigation, there are no concerns regarding the performance of the Oxoid Eravacycline disk.

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:

The FDA-identified interpretive criteria for eravacycline are listed in **Table 4**.

Table 4: FDA-Identified Interpretive Criteria for Eravacycline[1,2]

	Disk Diffusion (mm)		
Organisms	**S**	**I**	**R**
Enterobacteriaceae	≥15	-	-

[1] According to FDA STIC Website.
[2] The current absence of resistant isolates precludes defining any results other than "Susceptible". No resistance or intermediate interpretive criteria have been established.

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.