510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K231806

B Applicant

Oxoid Limited (Part of Thermo Fisher Scientific)

C Proprietary and Established Names

Thermo Scientific Oxoid Rezafungin Disc (5 µg) RZF5

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:

In this Traditional 510(k) submission, Oxoid Limited (Part of Thermo Scientific) seeks the following:

1. Obtain a substantial equivalence determination for rezafungin antimicrobial susceptibility test disk.
2. Establish a Pre-Determined Change Control Plan (PCCP) to address future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage.

B Measurand:

Rezafungin 5µg

C Type of Test:

Antimicrobial susceptibility test disk

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Thermo Scientific Oxoid Antimicrobial Susceptibility Test Discs are used in the semi-quantitative agar diffusion test method for *in vitro* susceptibility testing. Used in a diagnostic workflow to aid clinicians in determining potential treatment options for patients suspected of having a microbial infection, these disks are intended to determine susceptibility against microorganisms for which specific drugs have been shown to be active both clinically and *in vitro*.

The Thermo Scientific Oxoid Rezafungin Disc (5 µg) RZF5 can be used to determine susceptibility to Rezafungin against the following fungi for which Rezafungin has been shown to be active both clinically and *in vitro*:

Candida albicans

Candida glabrata

Candida parapsilosis

Candida tropicalis

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Not applicable.

IV Device/System Characteristics:

A Device Description:

Thermo Scientific Oxoid Rezafungin Disc (5µg) is a high quality 6mm diameter white filter paper disk that is impregnated with 5µg Rezafungin. The disks are clearly marked on both sides with RZF5, designating the agent and the drug content. The disks are supplied in plastic

cartridges containing 50 disks each. Thermo Scientific Oxoid Rezafungin Disc (5µg) is intended to be used for *in vitro* agar diffusion susceptibility testing.

B Principle of Operation:

A suitable therapeutic agent for *in vitro* use can be determined using filter paper disks impregnated with specified concentrations of antimicrobial agents placed on the surface of a suitable test medium. Pure cultures of clinical isolates are inoculated onto the test medium and the AST disk placed on the surface. 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 agents/organisms combination under test.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Fluconazole 25ug Bbl Sensi-disc

B Predicate 510(k) Number(s):

K082271

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K231806	Predicate: K082271
Device Trade Name	Thermo Scientific Oxoid Rezafungin Disc (5 µg) RZF5	Fluconazole 25 µg BBL sensi-disc (FCN25)
General Device Characteristic Similarities		
Intended Use/Indications For Use	Antimicrobial susceptibility test disks are used for *in vitro* susceptibility testing by standardized agar diffusion test procedures.	Same
Test Method	Antimicrobial susceptibility testing using paper disks impregnated with an antimicrobial agent	Same
Methodology	Disk diffusion susceptibility test protocol requires the user to determine categorical interpretations (S/I/R) using the measured zone diameters.	Same
Inoculum	Prepared from pure isolated colonies to match the turbidity	Same

Device & Predicate Device(s):	Device: K231806	Predicate: K082271
	equivalent of a 0.5 McFarland.	
Inoculum Method	Dip a sterile swab into the prepared inoculums, and streak an appropriate agar plate's surface three times. Add the disks impregnated with the antimicrobial agent to the surface of the plate. The temperature, atmospheric conditions and duration of incubation are dependent on the organism tested.	Same
Reading Method	The user will interpret the zone diameters according to established interpretive criteria for the drug.	Same
General Device Characteristic Differences		
Antibiotic	Rezafungin	Fluconazole
Concentration	5 µg	25 µg

VI Standards/Guidance Documents Referenced:

- CLSI M27M44S 3rd ed. *Performance Standards for Antifungal Susceptibility Testing of Yeasts* (August 2022).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Reproducibility was conducted at one internal site using 15 organisms, tested in triplicate with two disk lots on three separate days using one lot of media. Each test was visually read by three independent readers with results blinded, resulting in 270 data points for evaluation (15 organisms x 2 disk lots x 1 media x 3 days x 3 independent readers = 270 data points). Colony counts were performed on all isolates.

The reproducibility study included *Candida* spp. which consists of the following species: 4 isolates of *C. albicans*, 4 isolates of *C. parapsilosis*, 3 isolates of *C. tropicalis*, 4 isolates of *C. glabrata*.

Reproducibility was calculated as the percent of results which were within ±3 mm difference in zone diameter comparing test results with the modal zone diameter value. Results are shown in **Table 1** below.

Table 1: Reproducibility Summary

Between Disk Lots			Across Readers[1]			
Lot A	Lot B	All Lots	Reader#1	Reader#2	Reader#3	All Readers
100.0% (135/135)	100.0% (135/135)	100.0% (270/270)	100.0% (90/90)	100.0% (90/90)	100.0% (90/90)	100.0% (270/270)

[1]Two disk lots were read by each reader.

The reproducibility across disk lots is >95% which is 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 (QC) Testing:
   The CLSI-recommended quality control (QC) isolates, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida tropicalis* ATCC 750, and *Candida krusei* ATCC 6258 were tested. Five Oxoid disk lots were used. Each test was visually read by 5 independent readers, resulting in 316 Oxoid disk data points. The performance is shown in **Table 2** below.

Table 2: Quality Control Performance of Rezafungin (5 µg)

	Zone Diameter in millimeter (mm)[1]					
QC Organism	**Range**	**Oxoid Lot A**	**Oxoid Lot B**	**Oxoid Lot C**	**Oxoid Lot D**	**Oxoid Lot E**
C. albicans ATCC 90028 Expected Range: 13 – 20 mm	12					
	13		2	1		
	14		12	2		
	15	5	14	2	1	1
	16	4	4	1	1	1
	17	1			4	5
	18		1		4	2
	19				4	4
	20				1	2
	21					

QC Organism	Zone Diameter in millimeter (mm)[1]					
	Range	Oxoid Lot A	Oxoid Lot B	Oxoid Lot C	Oxoid Lot D	Oxoid Lot E
	22					
C. parapsilosis ATCC 22019 Expected Range: 9 – 16 mm	8					
	9		2			
	10	1	14	2		
	11	2	13	4	2	3
	12		3	1	4	4
	13		1		7	6
	14				3	1
	15				1	2
	16				1	2
	17					
	18					
C. tropicalis ATCC 750 Expected Range: 14 – 20 mm	13		1			
	14	1	12			
	15	4	10	3		
	16	4	7	3	1	2
	17	1	3		2	1
	18				7	7
	19				5	
	20				1	6
	21					
	22					
C. krusei ATCC 6258 Expected Range: 14 – 20 mm	13					
	14		14	1		
	15	3	16	4		
	16		1	2		
	17		2		2	
	18				6	5
	19				8	11
	20				1	1
	21					
	22					

ATCC=American Type Culture Collection
[1]Five Oxoid disk lots were tested (lot A, B, C, D and lot E)

Broth micro dilution (BMD) for QC isolates (*C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019) was performed as per CLSI M27 on every day of clinical study (**Table 3**).

Table 3: Quality Control Performance of Rezafungin (5 µg) by BMD Method

QC Organism	MIC (µg/mL)	Results
C. krusei ATCC 6258 Expected Range:	0.008	
	0.016	
	0.03	9
	0.06	14

QC Organism	MIC (µg/mL)	Results
0.016 – 0.12 µg/mL	0.12	
	0.25	
	0.5	
C. parapsilosis ATCC 22019 Expected Range: 0.25 – 2 µg/mL	0.12	
	0.25	
	0.5	7
	1	36
	2	
	4	
	8	

ATCC=American Type Culture Collection

The QC performance for both disk diffusion method and BMD method is > 95% and is 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.

Stability:
The sponsor provided data from real time and accelerated stability studies. The information is provided in the package insert. The real time stability test is on-going.

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   The qualitative Oxoid rezafungin 5 µg (RZF 5) disk diffusion results were compared to the qualitative reference broth microdilution (BMD) results to assess the categorical agreement (CA). The study was conducted at three testing sites. Three independent operators participated in reading of test results with isolates. Testing was performed with three lots of disks following the CLSI M44 guidelines for *Candida* spp. The reference broth microdilution (BMD) method was performed per CLSI M27 guidelines.

   Clinical:
   Clinical testing was performed using a total of 598 clinical isolates including: *C. albicans* (244 isolates), *C. glabrata* (144 isolates), *C. parapsilosis* (85 isolates), and *C. tropicalis* (125 isolates).

Performance results for the 598 clinical isolates are shown in **Table 4**.

Table 4. Performance of Oxoid Rezafungin Disk vs. Reference BMD

	Total	CA#	CA%	S (#)	NS (#)	VMJ	MAJ	MIN
Candida albicans ≥13 (S) only								
Clinical	244	242	99.2	243	1	1[1]	1	NA
Candida glabrata ≥15 (S) only								
Clinical	144	126	87.5	135	9	1[1]	17	NA
Candida parapsilosis ≥9 (S) only								
Clinical	85	85	100.0	85	0	0	0	NA
Candida tropicalis ≥14 (S) only								
Clinical	125	110	88.0	125	0	0	15	NA

[1]Due to the lack of an interpretive category other than susceptible for rezafungin and considering the potential VMJ error had MIC values that were one doubling dilution from the breakpoint and disk zone diameters that were ≤3 mm (i.e., one MIC doubling dilution equivalent) from the breakpoint, the adjusted potential VMJ error rate is 0%.
NA: Not Applicable

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

The performance of the Thermo Scientific Oxoid Rezafungin disk was compared to the reference MIC broth microdilution method. Category Agreement (CA) is when the Thermo Scientific Oxoid disk result interpretation agrees exactly with the MIC result interpretation. Due to the lack of an interpretive criterion other than susceptible, further analysis of categorical errors was performed and adjustments made by considering the disk zone diameter and MIC values compared to the breakpoints. Categorical errors that include MIC values that are one doubling dilution from the breakpoint and disk zone diameters that are ≤3 mm (i.e., one MIC doubling dilution equivalent) from the breakpoint are excluded in the adjusted calculation of errors and noted in a footnote in the performance table of the package insert.

The performance of the Thermo Scientific Oxoid Rezafungin disk when testing *C. albicans* is acceptable with 99.2% CA. The major error rate was 0.4% (1/243 susceptible isolates) and and the potential very major error rate was 100% (1/1 resistant isolates). Due to the lack of an interpretive criterion other than susceptible, the adjusted potential very major error rate is 0%, which is acceptable. The following footnote was included in the device labeling:

> *Due to the lack of an interpretive category other than susceptible for rezafungin and considering the potential VMJ error had MIC values that were one doubling dilution from the breakpoint and disk zone diameters that were ≤3 mm (i.e., one MIC doubling dilution equivalent) from the breakpoint, the adjusted potential VMJ error rate is 0%.*

The performance of the Thermo Scientific Oxoid Rezafungin disk when testing *C. glabrata* is 87.5% CA. The potential very major error rate was 100% (1/1 resistant isolate) and the major error rate was 12.6% (17/135 susceptible isolates) which does not meet FDA acceptance criteria of ≤3% major errors. Due to the lack of an interpretive criterion other than susceptible, the adjusted potential very major error rate is 0%, which is acceptable, and the

previously stated footnote was included in the device labeling. To address the major errors due to zone diameters ≤14 mm, the following limitation was included in the device labeling:

Isolates of C. glabrata that provide a disc zone of inhibition ≤ 14 mm should be tested by an alternative testing method prior to reporting results.

The performance of the Thermo Scientific Oxoid Rezafungin disk when testing *C. parapsilosis* is acceptable with 100% CA. There were no major or very major errors.

The performance of the Thermo Scientific Oxoid Rezafungin disk when testing *C. tropicalis* is 88.0% CA. The major error rate was 12.0% (15/125 susceptible isolates) which does not meet FDA acceptance criteria of ≤3% major errors. To address the major error rate due to zone diameters ≤13 mm, the following limitation was included in the device labeling:

Isolates of C. tropicalis that provide a disc zone of inhibition ≤ 13 mm should be tested by an alternative testing method prior to reporting results.

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 labelling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved".

Non-susceptible Isolates Tested:
Due to the lack of an interpretive category other than susceptible for rezafungin, the following limitation was included in 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.

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 susceptibility interpretive criteria for Rezafungin are listed below.

Table 5A. FDA-Identified Interpretive Criteria for Rezafungin (Disk Diffusion)

Organisms	Interpretive Criteria for Rezafungin (mm)[a]		
	Susceptible	Intermediate	Resistant
Candida abicans	≥13	-	-
Candida glabrata	≥15	-	-
Candida parapsilosis	≥9	-	-
Candida tropicalis	≥14	-	-

[a]FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria Website
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

Table 5B. FDA-Identified Interpretive Criteria for Rezafungin (MIC)

Organisms	Interpretive Criteria for Rezafungin (µg/mL)[a]		
	Susceptible	Intermediate	Resistant
Candida abicans	≤0.12	-	-
Candida glabrata	≤0.12	-	-
Candida parapsilosis	≤0.2	-	-
Candida tropicalis	≤0.12	-	-

[a]FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria Website
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

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 predetermined change control plan (PCCP)

that was reviewed and accepted by FDA, as described in the Antimicrobial Susceptibility Test (AST) System Devices – Updating Breakpoints in Device Labeling guidance. This PCCP 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 PCCP outlined the specific procedures and acceptance criteria that Oxoid Limited (Part of Thermo Fisher Scientific) intends to use to evaluate the Thermo Scientific Oxoid Rezafungin Disc (5 µg) RZF5 when revised breakpoints for rezafungin are published on the FDA STIC webpage. The PCCP included with the submission indicated that if specific criteria are met, Oxoid Limited (Part of Thermo Fisher Scientific) will update the Thermo Scientific Oxoid Rezafungin Disc (5 µg) RZF5 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.