510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K243738

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

The Sensititre YeastOne Susceptibility System with Micafungin in the dilution range of 0.008-16 µg/mL

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
NGZ	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 Sensititre YeastOne Susceptibility System with Micafungin in the dilution range of 0.008-16 µg/mL.

B Measurand:

Micafungin in the dilution range 0.008 to 16 µg/mL

C Type of Test:

Quantitative antifungal susceptibility test (AST) growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):

The Sensititre YeastOne Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of *Candida* spp.

B Indication(s) for Use:

The Sensititre YeastOne Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of *Candida* spp.

This 510(k) is for micafungin in the dilution range of 0.008-16 µg/mL for testing *Candida* spp. on The Sensititre YeastOne Susceptibility System.

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

Candida albicans

Candida glabrata

Candida guilliermondi

Candida krusei

Candida parapsilosis

Candida tropicalis

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The following limitation was applied to micafungin testing in the device labeling:

> *Studies of Voriconazole, Caspofungin, Fluconazole, Rezafungin, and Micafungin with Candida spp. were performed using the AIM autoinoculator inoculation method and the VIZION reading method only. The use of alternative inoculation methods or alternative reading methods when testing Voriconazole, Caspofungin, Fluconazole, Rezafungin, and Micafungin have not been evaluated.*

Due to the insufficient number of resistant *Candida* spp. evaluated, the following limitation statement was applied to micafungin testing in the device labeling:

> *The ability of the Sensititre YeastOne Susceptibility System to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing: Micafungin (0.008-16 µg/ml) and Candida guilliermondii, Candida krusei, and Candida parapsilosis. If a resistant isolate is encountered, it should be submitted to a reference laboratory for further testing.*

D Special Instrument Requirements:

Sensititre AIM for device inoculation
Sensititre Vizion digital viewing device

IV Device/System Characteristics:

A Device Description:

The Sensititre YeastOne Susceptibility System is a micro-version of the broth dilution susceptibility test performed in multi-well microtiter plates. Various antifungal agents are serially diluted to concentrations bridging the range of clinical interest in autoclaved diluent which contains a colorimetric growth indicating compound.

A standardized organism suspension is prepared using the Sensititre Yeast Susceptibility inoculum broth and 100 µL of the suspension is inoculated into the dried antifungal containing wells. After inoculation with a standardized suspension of organisms in inoculum medium and incubation at 35°C for 24 hours, the minimum inhibitory concentration (MIC) for the test organism is determined by observing the lowest antifungal concentration preventing the development of a pink or purple color change (as evidenced by no color change).

Yeast growth in the antifungal solutions will be evident as change in the colorimetric growth indicator from blue (negative – no growth) to pink/purple (positive – growth). Turbidity is not read, only color change is used as an indicator of growth.

B Principle of Operation:

Colorimetric test in which MICs are determined by determining the lowest concentration of antifungal agent that shows no color change indicating inhibition of growth of the organism. A color change from blue to pink indicates growth of the organism.

The Sensititre YeastOne panels can be read only with the Vizion digital viewing device which 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):

The Sensititre YeastOne Susceptibility System with Rezafungin in the dilution range of 0.008-8 µg/mL

B Predicate 510(k) Number(s):

K231433

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K243738	Predicate: K231433
Device Trade Name	The Sensititre YeastOne Susceptibility System with Micafungin in the dilution range of 0.008-16 µg/mL	The Sensititre YeastOne Susceptibility System with Rezafungin in the dilution range of 0.008-8 µg/mL
General Device Characteristic Similarities		
Intended Use	The Sensititre YeastOne Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of *Candida* spp.	Same
Technology	Colorimetric test in which MICs are determined by determining the lowest concentration of antifungal agent that shows no color change indicating inhibition of growth of the organism. A color change from blue to pink indicates growth of the organism.	Same
Test Panel	Each 96 well plate is precision dosed with selected antifungal agents, a stabilizer and the alamarBlue indicator then dried thereby stabilized. The fungal suspension in the appropriate broth is used to rehydrate the plate.	Same
Incubation	24 hours	Same
Read Method	Vizion	Same
General Device Characteristic Differences		
Antifungal and Dilution Range	Micafungin 0.008-16 µg/mL	Rezafungin 0.008-8 µg/mL
Indicated Species	*Candida albicans* *Candida glabrata*	*Candida albicans* *Candida glabrata*

	Candida guilliermondii *Candida krusei* *Candida parapsilosis* *Candida tropicalis*	*Candida parapsilosis*

VI Standards/Guidance Documents Referenced:

CLSI M27M44S, "Performance Standards for Antifungal Susceptibility Testing of Yeasts -3rd Edition", (August 2022)

CLSI M27, "Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts - 4th Edition", (November 2017)

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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   A reproducibility study of The Sensititre YeastOne Susceptibility System with Micafungin was performed at four sites using a panel of twelve (12) *Candida* isolates from indicated species (2 *Candida albicans*, 2 *Candida glabrata*, 1 *Candida guilliermondii*, 3 *Candida krusei*, 2 *Candida parapsilosis*, and 2 *Candida tropicalis*). In addition, three *Candida* isolates (1 *Candida lusitaniae*, and 2 *Candida auris*) were tested that are not intended for testing with this device. All isolates were tested in triplicate over three days and read visually with the Vizion. The Sensititre AIM autoinoculator was used for Sensititre plate inoculation. The mode MIC value was determined, and the reproducibility of the twelve (12) isolates was calculated based on MIC values falling within ±1 or ±2 doubling dilution of the mode MIC value. The reproducibility studies for both calculations demonstrated an acceptable performance of ≥95%.

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 CLSI-recommended quality control (QC) strains *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were tested at four sites. The QC strains were tested a minimum of 20 times per site and read visually with the Vizion. The QC strains were also tested with the reference method. The results demonstrate that The Sensititre YeastOne Susceptibility System with Micafungin produced quality control results within the recommended range >95% of the time (**Table 1**).

Table 1. Quality Control Results for *C. parapsilosis* and *C. krusei* with Micafungin with the Reference Method and Vizion

QC Organism	Expected Range (µg/mL)	Concentration (µg/mL)	Reference	Vizion
Candida parapsilosis ATCC 22019	0.5-2	≤0.25		
		0.5	32	
		1	34	79
		2	16	9
		≥4		
Candida krusei ATCC 6258	0.06-0.25	≤0.03		
		0.06	5	1
		0.12	49	86
		0.25	27	1
		≥0.5		

Inoculum Density: Inoculum density checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from cultures with appropriate inoculum densities were reported.

Purity Checks: Purity checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from pure cultures were reported.

Growth Failure: There were no growth failures on The Sensititre YeastOne Micafungin 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 YeastOne Susceptibility System with Micafungin was performed at one internal and three external sites. Results were compared to those obtained with the CLSI

broth microdilution reference method. Sensititre panels were inoculated using the AIM Autoinoculator and results were read visually by the Vizion only. Reference panels were inoculated according to recommendations in the CLSI M27 document and results were interpreted manually using a mirrored reader.

No inoculation system other than the AIM Autoinoculator and no read method other than Vizion were used in the comparative study. To address the inoculation method and read method limitation, the following limitation was updated in the device labeling, the updates are shown in **bold**:

Studies of Voriconazole, Caspofungin, Fluconazole, Rezafungin, ***and Micafungin*** *with Candida spp. were performed using the AIM autoinoculator inoculation method and the VIZION reading method only. The use of alternative inoculation methods or alternative reading methods when testing Voriconazole, Caspofungin, Fluconazole, Rezafungin,* ***and Micafungin*** *have not been evaluated.*

The testing conditions for the reference method consisted of the following:

- Media: Roswell Park Memorial Institute (RPMI) 1640 Culture Medium plus 0.2% glucose
- Inoculum: Inoculated per CLSI M27 guidelines
- Incubation: 35°C in a non-CO_2 incubator for 24 hours

Inoculation and incubation procedure for *Candida* spp.

- Media: Sensititre Yeast Susceptibility inoculum Broth
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared in 5 mL sterile water. Twenty (20) µL of the standardized suspension was transferred to 11 mL of Yeast Susceptibility Inoculum Broth. Susceptibility plates were inoculated with 100 µL of the final organism suspension using the Sensititre AIM Autoinoculator.
- Incubation: 35ºC in a non-CO_2 incubator for 24 hours

A total of 528 clinical isolates comprised of 142 *C. albicans* isolates, 98 *C. glabrata* isolates, 28 *C. guilliermondii* isolates, 80 *C. krusei* isolates, 91 *C. parapsilosis* isolates, 89 *C. tropicalis* isolates as well as 84 challenge isolates comprised of 21 *C. albicans* isolates, 27 *C. glabrata* isolates, 1 *C. guilliermondii* isolate, 8 *C. krusei* isolates, 10 *C. parapsilosis* isolates, 17 *C. tropicalis* isolates were evaluated with the Vizion and the results were provided in **Table 2**.

For *C. albicans* read using the Vizion, the combined clinical and challenge results (163 isolates) were acceptable at 99.4% and 98.2% for EA and CA, respectively. There were 3 minor errors, no major errors, and no very major errors.

For *C. glabrata* read using the Vizion, the combined clinical and challenge results (125 isolates) were acceptable at 100% and 96.8% for EA and CA, respectively. There were 4 minor errors, no major errors, and no very major errors.

For *C. guilliermondii* read using the Vizion, the combined clinical and challenge results (29 isolates) were acceptable at 96.6% and 100% for EA and CA, respectively. There were no minor errors, no major errors, and no very major errors.

For *C. krusei* read using the Vizion, the combined clinical and challenge results (88 isolates) were acceptable at 98.9% and 97.7% for EA and CA, respectively. There were 2 minor errors, no major errors, and no very major errors.

For *C. parapsilosis* read using the Vizion, the combined clinical and challenge results (88 isolates) were acceptable at 99.0% and 99.0% for EA and CA, respectively. There was 1 minor error, no major errors, and no very major errors.

For *C. tropicalis* read using the Vizion, the combined clinical and challenge results (88 isolates) were acceptable at 99.1% and 98.1% for EA and CA, respectively. There were 2 minor errors, no major errors, and no very major errors.

Due to the insufficient number of resistant isolates evaluated for some *Candida* spp., the following limitation was applied to micafungin testing in the device labeling:

The ability of the Sensititre YeastOne Susceptibility System to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing: Micafungin (0.008-16 µg/ml) and Candida guilliermondii, Candida krusei, and Candida parapsilosis. If a resistant isolate is encountered, it should be submitted to a reference laboratory for further testing.

Table 2. Micafungin Performance of *Candida* spp. Read by Vizion

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
***Candida albicans* [≤ 0.25 (S), 0.5 (I), ≥1 (R)]**													
Clinical	142	141	99.3	97	95	97.9	139	97.9	6	132	3	0	0
Challenge	21	21	100	12	11	91.7	21	100	0	21	0	0	0
Combined	163	162	99.4	109	106	97.3	160	98.2	6	153	3	0	0
***Candida glabrata* [≤ 0.06 (S), 0.12 (I), ≥0.25 (R)]**													
Clinical	98	98	100	83	83	100	94	95.9	4	92	4	0	0
Challenge	27	27	100	20	20	100	27	100	11	16	0	0	0
Combined	125	125	100	103	103	100	121	96.8	15	108	4	0	0
***Candida guilliermondii* [≤ 2 (S), 4 (I), ≥8 (R)]**													
Clinical	28	27	96.4	28	27	96.4	28	100	0	28	0	0	0
Challenge	1	1	100	1	1	100	1	100	0	1	0	0	0
Combined	29	28	96.6	29	28	96.6	29	100	0	29	0	0	0
***Candida krusei* [≤ 0.25 (S), 0.5 (I), ≥1 (R)]**													
Clinical	80	79	98.8	80	79	98.8	78	97.5	1	78	2	0	0
Challenge	8	8	100	8	8	100	8	100	0	8	0	0	0
Combined	88	87	98.9	88	87	98.9	86	97.7	1	86	2	0	0
***Candida parapsilosis* [≤ 2 (S), 4 (I), ≥8 (R)]**													
Clinical	91	90	98.9	91	90	98.9	90	98.9	0	91	1	0	0
Challenge	10	10	100	10	10	100	10	100	0	10	0	0	0
Combined	101	100	99.0	101	100	99.0	100	99.0	0	101	1	0	0
***Candida tropicalis* [≤ 0.25 (S), 0.5 (I), ≥1 (R)]**													
Clinical	89	88	98.9	89	88	98.9	87	97.8	2	86	2	0	0

Challenge	17	17	100	15	15	100	17	100	0	17	0	0	0
Combined	106	105	99.1	104	103	99.0	104	98.1	2	103	2	0	0

EA – Essential Agreement
CA – Categorical Agreement
S – Susceptible
maj – Major Discrepancies
EVAL – Evaluable MICs
R – Resistant
min – Minor 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 two serial two-fold dilution of the antifungal agent. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is more than 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.

MIC Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained from the Vizion for *Candida* spp. 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 or 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. Trending that shows higher or lower MIC values compared to the reference is addressed in the labeling.

Evaluation of results for *Candida* spp. with micafungin using the Vizion are summarized in **Table 3**. No trending was observed.

Table 3. Micafungin Trending Analysis for *Candida* spp. with Vizion

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No.	≥ 1 Dilution Higher No. (%)	Percent Difference (95% CI)	Trending Noted
Candida albicans	143	56 (39.2)	54	33 (23.1)	-16% (-26% to -5%)	No
Candida glabrata	122	47 (38.5)	51	24 (19.7)	-19% (-30% to -7%)	No
Candida guilliermondii	29	5 (17.2)	19	5 (17.2)	0% (-20% to 20%)	No
Candida krusei	88	8 (9.1)	51	29 (33.0)	24% (12% to 35%)	No
Candida parapsilosis	101	15 (14.9)	47	39 (38.6)	24% (12% to 35%)	No
Candida tropicalis	106	22 (20.8)	38	46 (43.4)	23% (10% to 34%)	No

Testing/Reporting MICs 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 included in the Warnings and Precautions section of the device labeling to address testing and reporting of non-indicated species:

> *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.*

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 4. FDA-Recognized Interpretive Criteria for Micafungin

Organism	Minimum Inhibitory Concentrations (µg/mL)[a]		
	Susceptible	Intermediate	Resistant
C. albicans	≤0.25	0.5	≥1
C. glabrata	≤0.06	0.12	≥0.25
C. guilliermondii	≤2	4	≥8
C. krusei	≤0.25	0.5	≥1
C. parapsilosis	≤2	4	≥8
C. tropicalis	≤0.25	0.5	≥1

[a] According to the 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 incorporated by reference a breakpoint change protocol that was reviewed and accepted by FDA in submission K231994 cleared on August 25, 2023. This referenced 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/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria). The referenced protocol outlined the specific procedures and acceptance criteria that Thermo Fisher Scientific intends to use to evaluate The Sensititre YeastOne Susceptibility System with Micafungin in the dilution range of 0.008-16 µg/mL when revised breakpoints for micafungin are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Thermo Fisher Scientific will update the micafungin 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.