510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K221899

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

The Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16 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 clearance for the YeastOne Susceptibility System with Caspofungin for a new dilution range of 0.015 – 16 µg/mL and with updated breakpoints for *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis*.

B Measurand:

Caspofungin at concentrations of 0.015-16 µg/mL

C Type of Test:

Quantitative Antifungal Susceptibility test, growth based

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

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

This 510(k) is for Caspofungin with new FDA breakpoints and indications for testing *Candida* spp on the Sensititre YeastOne Susceptibility System.

Caspofungin 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 krusei

Candida parapsilos

Candida tropicalis

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Limitations:

- Studies of Caspofungin 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 Caspofungin have not been evaluated.

- Due to categorical agreeement below 90% with the Sensititre YeasOne Susceptibility System when compared to the CLSI antifungal broth microdilution method caused by the occurrence categorical errors and to avoid potential false susceptible results, perform an alternative method of testing prior to reporting results for the following antibiotic/organism combination(s): Caspofungin: *Candida glabrata* when the MIC is ≤0.12 µg/ml (if critical to patient care).

- 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: Caspofungin (0.015-16 µg/ml) and *Candida albicans*, *Candida krusei*, *Candida*

parapsilosis, *Candida glabrata* and *Candida tropicalis*. If a resistant isolate is encountered, it should be submitted to a reference laboratory for further testing.

D Special Instrument Requirements:

Sensititre Vizion

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.

There are several differences between the previously cleared version of the Sensititre YeastOne Susceptibility System with Caspofungin and the current device, including: 1) the caspofungin dilution range (previously cleared device - 0.008 to 16 µg/mL, current device 0.015-16 µg/mL), 2) inoculator (previously cleared device AIM/Autoculator and Manual pipettor, current device AIM/Autoinoculator only), 3) only the VIZION reading method has been used in the current study, and 4) breakpoints have been updated according to the FDA-recognized breakpoints in the STIC website for all indicated *Candida* species.

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 viewer 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):
Sensititre YeastOne Susceptibility System with Voriconazole in the dilution range of 0.008 - 8 µg/mL

B Predicate 510(k) Number(s):
K211539

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device K221899	Predicate K211539
Device Trade Name	Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16 µg/mL.	Sensititre YeastOne Susceptibility System with Voriconazole in the dilution range of 0.008-8 µg/mL
General Device Characteristic Similarities		
Intended Use	Sensititre YeastOne Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of Candida spp.	Same
Organisms Tested	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.
Inoculation Method	AIM autoinoculator	Same
Medium	Sensititre yeast susceptibility inoculum broth.	
Incubation time	24 h	Same

Incubation Temperature	35°C	Same.
Reading Method	Vizion	Same.
General Device Characteristic Differences		
Antifungal Agent	Caspofungin in the dilution range of 0.015-16 µg/mL.	Voriconazole in the dilution range of 0.008 – 8 µg/mL
Indicated Species	*Candida albicans* *Candida glabrata* *Candida krusei* *Candida parapsilosis* *Candida tropicalis*	*C. albicans,* *C.krusei,* *C. parapsilosis*

VI Standards/Guidance Documents Referenced:

CLSI. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*; 4th ed. CLSI standard M27. 2017

CLSI. *Performance Standards for Antifungal Susceptibility Testing of Yeasts.* 1st ed. CLSI supplement M60. 2017

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study of the Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16 µg/mL was performed from 2015-2016. Testing was performed at 3 sites with isolates tested in triplicate on three separate days Testing was performed using AIM autoinoculator method and the VIZION reading method only.

The following indicated isolates with known on-scale results were evaluated including *Candida parapsilosis*, *Candida krusei*, *Candida tropicalis*, *Candida glabrata*, *Candida albicans*.

The mode was determined and the reproducibility was calculated based on +/- one dilution and +/- two dilutions of the mode. The best case reproducibility demonstrated acceptable performance at >95% based on +/- one dilution of the mode. Both the best and worst case reproducibility were >95% based on +/- 2 dilutions of the mode. (**Table 1**).

Table 1. Reproducibility of Sensititre YeastOne with Caspofungin 0.015-16 µg/mL

Caspofungin	Reproducibility based on +/- 1 dilution of the mode	Reproducibility based on +/- 2 dilutions of the mode
Best Case	95.1%	100%
Worst Case	94.6%	99.6%

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 strains recommended by CLSI were tested with Caspofungin at three sites. The QC organisms tested were *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258. Testing was performed each day of clinical testing and was performed a sufficient number of times (at least 20 times/site) using both the Sensititre YeastOne panel and the reference method.

   Testing was performed using the AIM autoinoculator inoculation method only. The Sensititre YeastOne panels were read using the Vizion only and the CLSI reference panels were read manually using the mirrored reader at 24 hours.

   Results obtained with the two QC strains were acceptable and demonstrated that the panel provides results within the expected range for greater than 95% of tests (**Table 2**).

Table 2. Results of QC Testing for the YeastOne with Caspofungin (0.015-16µg/ml).

QC Organism	Expected Range (µg/mL)[a]	Concentration (µg/mL)	Reference BMD (24 hrs)	Sensititre YeastOne (24 hrs)
C. parapsilosis ATCC 22019	0.25-1 µg/mL	**0.015**	-	-
		0.03	-	-
		0.06	-	-
		0.12	-	1
		0.25	37	31
		0.5	21	26
		1	2	2
		2	-	-
		4	-	-
		8	-	
		>16	-	-
C. krusei ATCC 6258	0.12-1 µg/mL	**0.015**	-	-
		0.03	-	-
		0.06	-	-
		0.12	13	13
		0.25	43	44
		0.5	2	3

QC Organism	Expected Range (µg/mL)[a]	Concentration (µg/mL)	Reference BMD (24 hrs)	Sensititre YeastOne (24 hrs)
		1	-	-
		2	-	-
		4	-	-
		8	-	-
		>16	-	-

[a]As indicated in: CLSI. *Performance Standards for Antifungal Susceptibility Testing of Yeasts.* 2nd ed. CLSI supplement M60.

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.

Purity Check: Purity Checks were performed on all isolates following panel inoculation. Only results from pure cultures were evaluated.

Growth Failure: There were no growth failures on the Sensititre YeastOne Caspofungin panels.

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Clinical testing of Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16 µg/mL was performed in 2015-2016 at two external sites and one internal site.

   Results obtained with Sensititre YeastOne Susceptibility System with Caspofungin (0.015-16 ug/mL) were compared to results obtained with the CLSI antifungal broth microdilution reference panel with Caspofungin.

   Sensititre YeastOne panels were inoculated using AIM Autoinoculator and results were interpreted using the Vizion only. To address the inoculation and reading methods for the Sensititre YeastOne panels, the following limitation was added in the device labeling:

   > *"Studies of Capofungin 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 have not been evaluated".*

Reference panels were inoculated according to recommendations in the M27 CLSI document and results were interpreted manually using a mirrored reader. The testing conditions for the reference method consisted of the following:

Media: Roswell Park Memorial Institure (RPMI) 1640 Culture Medium plus 0.2% glucose.
Inoculum Preparation: per CLSI M27 4th Edition (Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts).
Incubation: 24 hours at 35 °C in ambient air.

The testing conditions for the Sensititre YeastOne Susceptibility System with Capofungin (0.015-16 µg/ml) consisted of the following:

Media: Sensititre Yeast Susceptibility inoculum Broth.
Inoculum Preparation: A standardized suspension (0.5 McFarland) was prepared from a pure 24-hour culture of the yeast isolate in sterile water. Twenty (20) µL of the yeast suspension was inoculated into 11 mL of Yeast Susceptibility Inoculum Broth to create a suspension containing 1.5 to 8.0 X 10^3 CFU/mL. One hundred (100) µL of the broth suspension was inoculated into the plate using the AIM/Autoinoculator.

Incubation: 24 hours at 35 °C in ambient air.

Reading: VIZION only.

A total of 336 (241 clinical and 95 challenge) isolates of *Candida* spp were evaluated with both the Sensititre YeastOne Susceptibility panels and the reference panels including 99 isolates of *C. albicans* (61 clinical isolates, 38 challenge), 67 isolates of *C. krusei* (60 clinical, 7 challenge), 71 isolates of *C. parapsilosis* (61 clinical, 10 challenge), 46 *C. tropicalis* (30 clinical, 16 challenge) and 53 *C. glabrata* (29 clinical, 24 challenge).

Table 3. Performance of YeastOne Susceptibility System with Caspofungin (0.015-16 µg/mL)

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vm j
***Candida albicans* (≤0.12, 0.5, ≥1 µg/mL)**													
Clinical	61	61	100.0	55	55	100.0	61	100.0	0	61	0	0	0
Challenge	38	38	100.0	37	37	100.0	38	100.0	0	38	0	0	0
Total	99	99	**100.0**	92	92	100.0	99	**100.0**	0	99	0	0	0
***Candida krusei* (≤0.25, 0.5 ≥1 µg/mL)**													
Clinical	60	60	100.0	60	60	100.0	57	95.0	0	57	3	0	0
Challenge	7	7	100.0	7	7	100.0	2	28.5	0	7	5	0	0
Total	67	67	**100.0**	67	67	100.0	59	**88.1**	0	64	8	0	0
***Candida parapsilosis* (≤2, 4, ≥8 µg/mL)**													
Clinical	61	61	100.0	61	61	100.0	61	100.0	0	61	0	0	0
Challenge	10	10	100.0	10	10	100.0	10	100.0	0	10	0	0	0
Total	71	71	**100.0**	71	71	100.0	71	**100.0**	0	71	0	0	0
***Candida glabrata* (≤0.12, 0.25, ≥0.5 µg/mL)**													
Clinical	29	29	100.0	29	29	100.0	26	89.7	2	27	3	0	0
Challenge	24	24	100.0	24	24	100.0	17	70.8	2	22	5	1	1
Total	53	53	**100.0**	53	53	100.0	43	**81.1**	4	49	8	1	1
***Candida tropicalis* (≤0.25, 0.5, ≥1 µg/mL)**													

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Clinical	30	29	96.7	30	29	96.7	30	100.0	0	30	0	0	0
Challenge	16	15	93.8	15	14	93.3	16	100.0	0	16	0	0	0
Total	46	44	**95.7**	45	43	95.6	46	**100.0**	0	46	0	0	0

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable Isolates
R – Resistant Isolates
min – minor errors
maj – major errors
vmj – very major errors
S – Susceptible Isolates

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre YeastOne Susceptibility System with Caspofungin are within plus or minus two serial two-fold dilutions of the antibiotic. Evaluable results are those that are on-scale for both the reference method and the Sensititre YeastOne Susceptibility System with Caspofungin. Evaluable results also include results 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 provided by the Sensititre YeastOne Susceptibility System with Caspofungin.

Performance for the 336 clinical and challenge isolates are shown in **Table 3** and summarized below:

- For *C. krusei,* the EA was acceptable at 100%. The CA was 88.1% mainly due to a high number of minor errors. There were no major or very major errors observed. Since the EA of evaluable results for *C. krusei* was acceptable at 100%, the low CA is considered acceptable.

- For *C. glabrata*, the EA was acceptable at 100%; however, the CA was not acceptable at 81.1%. There were 8 minor errors (8/53 = 15%), one major error (1/49 susceptible isolates = 2%), and one very major error (1/4 resistant isolates = 25%) which does not meet FDA's acceptance criteria of ≤2% VMJ error rate. To address the occurrence of very major errors with Caspofungin, the following limitation was added to the device labeling:

  "Due to categorical agreement below 90% with the Sensititre YeastOne Susceptibility System when compared to the CLSI antifungal broth microdilution method caused by the occurrence of categorical errors and to avoid potential false susceptible results, perform an alternative method of testing prior to reporting results for the following antibiotic/organism combination(s): Caspofungin: Candida glabrata when the MIC is ≤ 0.12µg/ml".

- For *C. albicans*, *C. parapsilosis* and *C. tropicalis*, the EA and CA were >90% and considered acceptable. There were no minor, major, or very major errors.

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 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.*

Resistant Isolates:

A total of 336 clinical and challenge *Candida* spp isolates were tested when the Sensititre YeastOne System with Caspofungin (0.015-16 µg/mL) was compared to the reference method. However, only 4 resistant isolates were available for *C. glabrata*, while the remaining *Candida* species had no resistant isolates available during the comparative study. To address the lack of resistant strains encountered during the clinical evaluation, the following limitation was added 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: Caspofungin in the dilution range 0.015-16 µg/ml and Candida albicans, Candida krusei, Candida parapsilosis, Candida glabrata and Candida tropicalis. If a resistant isolate is encountered, it should be submitted to a reference laboratory for further testing*".

Resistance Mechanisms:

Challenge isolates harboring the resistance mechanisms against Caspofungin which have been shown to be active were not tested. This was addressed in the device labeling by adding the following footnote under the performance table:

> "*The performance of the Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16 µg/mL was not evaluated with challenge isolates harboring resistance mechanisms listed in the FDA drug label*".

Trending:

A trending analysis was conducted using the combined data (clinical and challenge) obtained for Vizion read for each species. 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. Trending that showed higher or lower MICs values compared to the reference is addressed in the labeling.

Table 4. Trending Observed for *Candida species* tested with the Sensititre YeastOne System with Caspofungin 0.015-16 µg/mL.

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference[1] (CI)	Trending Noted
C. krusei	67	5 (7.46%)	45 (67.16%)	17 (25.37%)	17.92% (5.4%, 30.92%)	No
C. tropicalis	45	5 (11.11%)	15 (33.33%)	25 (55.56%)	44.4% (25.5%, 59.3%)	Yes
C. parapsilosis	71	10 (14.08%)	44 (61.97%)	17 (23.94%)	9.9% (-3.2%, 22.6)	No
C. albicans	98	5 (5.10%)	31 (31.63%)	62 (63.27%)	58.2% (46.5%, 67.5%)	Yes
C. glabrata	53	5 (9.43%)	21 (39.62%)	27 (50.94%)	41.5% (24.5%, 55.5%)	Yes

[1]A positive % difference indicates higher MIC when compared to the reference method.

High trending was observed for *C. tropicalis*, *C. albicans* and *C. glabrata* (Table 4). To address the high trend observed with these organisms, the following footnote was added to the performance table in the device labeling:

> *"The Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16 µg/mL MIC values tended to be in exact agreement or at least one doubling dilution higher for C. tropicalis, C. albicans and C. glabrata compared to the CLSI broth microdilution reference 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 5. FDA-Recognized Interpretive Criteria for Caspofungin[a]

Organism	Interpretive Criteria for Caspofungin (µg/mL)		
	Susceptible	Intermediate	Resistant
C. albicans	≤0.25	0.5	≥1
C. krusei	≤0.25	0.5	≥1
C. tropicalis	≤0.25	0.5	≥1
C. glabrata	≤0.12	0.25	≥0.5
C. parapsilosis	≤2	4	≥8

[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 Thermo Fisher Scientific intends to use to evaluate the Sensititre YeastOne Susceptibility System with Caspofungin in the dilution range of 0.015-16µg/mL when revised breakpoints for Caspofungin 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 Caspofungin 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.