510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K211539

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

Sensititre YeastOne Susceptibility System with Voriconazole in the dilution range of 0.008-8 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 Voriconazole for a new dilution range of 0.0008 – 8 µg/mL and with revised breakpoints for *C. albicans, C. krusei,* and *C. parapsilosis*.

B Measurand:

Voriconazole at concentrations of 0.008 to 8 µg/mL

C Type of Test:

Quantitative Antifungal Susceptibility test, growth based

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

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 with Voriconazole in the dilution range of 0.008 - 8 µg/mL is an in vitro diagnostic product for clinical susceptibility testing of *Candida* spp.

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

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

Candida albicans
Candida krusei
Candida parapsilosis

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

Limitations
Studies of Voriconazole 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.

Due to the low performance of voriconazole with *C. tropicalis,* isolates of *C. tropicalis* should be tested with an alternate method.

D Special Instrument Requirements:

Sensititre Vizion

IV Device/System Characteristics:

A Device Description:
The YeastOne Susceptibility System with Voriconazole 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 in YeastOne inoculum broth and 100 µL of the suspension is inoculated into the dried anti-fungal 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. 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.

For voriconazole, trailing growth is frequently observed. Trailing appears as a slight color change that persists above the MIC and is often identical for several or all concentrations above the MIC. The MIC is read as the first well showing a less intense color change compared to the more positive growth wells of the lower concentrations.

There are several differences between the previously cleared version of YeastOne Susceptibility System with Voriconazole and the current device including 1) the voriconazole dilution range (previously cleared device - 0.008 to 16 µg/mL, current device 0.008 to 8 µg/mL), 2) incubation time, 3) breakpoints for all indicated species, and 4) indicated species (currrent device is not indicated for *C. tropicalis*).

B Principle of Operation:

The 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 determined MIC results.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Sensititre Yeastone Susceptibility Plates

B Predicate 510(k) Number(s):
K133038

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device K211539**	**Predicate K133038**
Device Trade Name	Sensititre YeastOne Susceptibility System with Voriconazole in the dilution range of 0.008-8 µg/mL	Sensititre YeastOne Susceptibility Plates
General Device Characteristic Similarities		
Intended Use/Indications For Use	Sensititre YeastOne Susceptibility plates are designed for *in vitro* use in determining quantitative antifungal susceptibilities (MIC) of *Candida* species	Same
Specimen	*Candida* spp. isolated colonies from pure	Same

	culture	
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. A color change from blue to pink indicates growth of the organism	Same
Inoculation Method	AIM autoinculator	Same
Incubation	24 hours	Same
Incubation Temperature	34 – 36 °C	Same
Incubation Atmosphere	Ambient Air	Same
Reading Method	Vizion	Same
General Device Characteristic Differences		
Antifungal Agent	Voriconazole 0.008 – 8 µg/mL	Micafungin 0.008 – 8 µg/mL
Indicated Species	*C. albicans, C.krusei, C. parapsilosis*	*C. albicans, C.krusei, C. parapsilosis, C. tropicalis*

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 Sensititre YeastOne with Voriconazole was performed at four sites with isolates tested in triplicate on three separate days. A total of ten isolates were evaluated including *C. parapsilosis* (2 isolates), *C. krusei* (3 isolates), *C. tropicalis* (2 isolates), *C. albicans* (2 isolates) and *C. guilliermondii* (1 isolate) for a total of 360 data points. One

isolate of *C. albicans* had a mode MIC that was off-scale and was removed from the evaluation. *C. guilliermondii* is not included in the intended use of the Sensititre YeastOne with Voriconazole, however, *C. guilliermondii* is included in the list of organisms for which voriconazole shows in vitro activity according to the drug label. The inclusion of *C. guilliermondii* is acceptable.

Due to performance issues (see below), *C. tropicalis* was removed as an indicated species. Even without inclusion of the two *C. tropicalis* isolates, the reproducibility testing for all isolates was determined to be acceptable. Best case and worst case scenario reproducibility was calculated at 100% and 94.7%, respectively, for all isolates.

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 voriconazole at four sites. The QC organisms tested were *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258. Testing was performed daily and was performed a sufficient number of times (at least 20 times/site) using both the YeastOne panel and the reference method. The YeastOne panels were read using the Vizion and reference panels were read manually using the mirrored reader. 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 1 below).

Table 1. Results of QC Testing for Voriconazole

QC Organism	Voriconazole Range (µg/mL)[a]	Concentration (µg/mL)	Reference	Sensititre VIZION
C. parapsilosis ATCC 22019	0.016-0.12 µg/mL	≤0.008	-	-
		0.015	5	15
		0.03	42	54
		0.06	34	12
		0.12	1	
		0.25		
		0.5		
		1		
		2		
		4		
		8	1	1
		>8		

QC Organism	Voriconazole Range (µg/mL)[a]	Concentration (µg/mL)	Reference	Sensititre VIZION
C. krusei ATCC 6258	0.06-0.5 µg/mL	≤0.008	-	-
		0.015	-	-
		0.03	-	-
		0.06	10	
		0.12	32	2
		0.25	38	71
		0.5	1	9
		1	-	-
		2	-	-
		4	-	-
		8	-	-
		>8	-	-

[a] As indicated in: CLSI. *Performance Standards for Antifungal Susceptibility Testing of Yeasts.* 1st ed. CLSI supplement M60. 2017

Inoculum Density: Inoculum density checks were performed a sufficient number of times; overall inoculum density results were acceptable.

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 panels.

6. Detection Limit:
   Not Applicable

7. Assay Cut-Off:
   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Testing of voriconazole was performed at three external sites and one internal site. Results obtained with YeastOne Susceptibility System with Voriconazole were compared to results obtained with the CLSI antifungal broth microdilution reference panel with voriconazole. YeastOne panels were inoculated using AIM Autoinoculator and results were interpreted using the Vizion. Reference panels were inoculated according to recommendations in the M27 CLSI document and results were interpreted manually using a mirrored reader. To address the inoculation and read methods for the YeastOne panels, the sponsor included the following limitation in the device labeling:

   > *Studies of Voriconazole 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.*

The MIC result range for YeastOne Susceptibility System with Voriconazole is ≤0.08 to ≥8 µg/mL.

The testing conditions for the reference method consisted of the following:
Media: RPMI Culture Media
Inoculum: per CLSI M27
Incubation: 24 hours at 35 °C in ambient air.

The testing conditions for the YeastOne Susceptibility System with Voriconazole consisted of the following:
Media: YeastOne Inoculum Broth
Inoculum: A standardized suspension (0.5 McFarland) suspension was prepared from a pure 24-hour culture of the yeast isolate in sterile water. Twenty microliters of the yeast suspension was inoculated into 11 mL of YeastOne Inoculum Broth to create a suspension containing 1.5 to 8.0 X 10^3 CFU/mL. One hundred microliters of the broth suspension was inoculated into the plate using the AIM/Autoinoculator.
Incubation: 24 hours at 35 °C in ambient air

A total of 165 isolates of *C. albicans* (135 clinical isolates, 30 challenge), 88 isolates of *C. krusei* (79 clinical, 9 challenge), 104 isolates of *C. parapsilosis* (84 clinical 20 challenge) and 104 *C. tropicalis* (82 clinical, 22 challenge) were evaluated.

For *C. krusei* EA was acceptable; a slightly reduced CA for *C. krusei* (89.8%) was determined to be due to increased minor errors, there were no major or very major errors observed. Since the EA of evaluable results for *C. krusei* was acceptable at 98.9%, the reduced CA is considered acceptable. For *C. parapsilosis*, EA and CA were acceptable and there were no major or very major errors. For *C. albicans*, EA and CA were acceptable, there was one very major error which was considered to be related to incorrect interpretation of the reference method because of trailing endpoints (see below) and was considered a random error. Results for *C. albicans* were acceptable.

For *C. tropicalis* EA and CA were low at 89.4% and 67.3%, respectively. The low CA resulted partly from a high percentage of minor errors (28.8%); the major error rate was acceptable at 2.5%. The very major error rate was increased at 13.3% (2 very major errors/15 resistant strains) observed at a single site. The CLSI M27 document indicates that *C. albicans* and *C. tropicalis* have been observed to exhibit significant trailing with the azole antifungals with the broth microdilution reference method and may result in incorrect MIC determination. The interpretation protocols provided to the testing sites were reviewed for both the YeastOne Susceptibility System with Voriconazole and the CLSI broth microdilution reference method to assess the possibility of incorrect interpretation of MIC endpoints. After review, it was determined that all protocols included the correct interpretation methods. Documentation from the site for which very major errors were observed confirmed correct understanding of endpoint interpretation.

To address the low performance for *C. tropicalis,* the sponsor removed *C. tropicalis* as an indicated species for the assay and included the following limitation in the device labeling:

Due to the low performance of voriconazole with C. tropicalis, isolates of C. tropicalis should be tested with an alternate method.

Table 2. Performance of YeastOne Susceptibility System with Voriconazole for *Candida* spp.

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
***C. albicans* (≤0.12, 0.25 – 0.5, ≥1 µg/mL)**													
Clinical	135	126	93.3	72	63	87.5	131	97.0	13	116	3	0	1
Challenge	30	30	100.0	20	20	100.0	27	90.0	3	22	3	0	0
Total	165	156	94.5	92	83	90.2	158	95.8	16	138	6	0	1
***C. krusei* (≤0.5, 1 ≥2 µg/mL)**													
Clinical	79	78	98.7	79	78	98.7	70	88.6	5	72	9	0	0
Challenge	9	9	100.0	9	9	100.0	9	100.0	1	8	0	0	0
Total	88	87	98.9	88	87	98.9	79	89.8	6	80	9	0	0
***C. parapsilosis* (≤0.12, 0.25 – 0.5, ≥1 µg/mL)**													
Clinical	84	84	100.0	63	63	100.0	82	97.6	2	82	2	0	0
Challenge	20	20	100.0	15	15	100.0	19	95.0	3	15	1	0	0
Total	104	104	100.0	78	78	100.0	101	97.1	5	97	3	0	0
***C. tropicalis* (≤0.12, 0.25 – 0.5, ≥1 µg/mL)**													
Clinical	82	71	86.6	78	67	85.9	52	63.4	11	66	26	2	2
Challenge	22	22	100.0	20	20	100.0	18	81.8	4	14	4	0	0
Total	104	93	89.4	98	87	88.8	70	67.3	15	80	30	2	2

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 YeastOne Susceptibility System with Voriconazole 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 YeastOne Susceptibility System with Voriconazole. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by YeastOne Susceptibility System with Voriconazole.

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 3. Trending Observed for *C. albicans, C. krusei, and C. parapsilosis* with Voriconazole.

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
C. albicans	131	76 (58.0)	28 (21.4)	27 (20.6)	-37.4 (-47.5 to -25.9)	Yes Low
C. krusei	88	12 (13.6)	29 (33.0)	47 (53.4)	39.8 (26.3 to 51.3)	Yes High
C. parapsilosis	95	44 (46.3)	33 (34.7)	18 (19.0)	-27.4 (-39.3 to -14.1)	No

For voriconazole, low trending was observed for *C. albicans* and high trending was observed for *C. krusei* and *C. tropicalis.* Due to performance issues, *C. tropicalis* was removed as an indicated species.

To address trending, the sponsor included the following footnote to the performance table in the device labeling:

> *YeastOne voriconazole MIC values tended to be in exact agreement or at least one doubling dilution lower for C. albicans, and at least one doubling dilution higher for C. krusei compared to the CLSI broth microdilution reference method.*

Testing/Reporting MIC for Non-indicated Species:
For this review, the interpretative 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:

> *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 4. FDA-Identified Interpretive Criteria for Voriconazole[a]

Organism	Interpretive Criteria for Voriconazole (µg/mL)		
	Susceptible	Intermediate	Resistant
C. albicans	≤0.12	0.25-0.5	≥1
C. krusei	≤0.5	1	≥2
C. parapsilosis	≤0.12	0.25-0.5	≥1

[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 YeastOne Susceptibility System with Voriconazole in the dilution range of 0.008-8 µg/mL when revised breakpoints for voriconazole 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 voriconazole 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.