

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY**

**A. 510(k) Number:**

K151923

**B. Purpose for Submission:**

To obtain a substantial equivalence determination for the addition of Micafungin to the VITEK<sup>®</sup> 2 and VITEK<sup>®</sup> 2 Compact Systems Antimicrobial Susceptibility Test (AST) Systems

**C. Measurand:**

The VITEK 2 AST Yeast card contains the following concentration of Micafungin: 0.06, 0.25, 1 and 4µg/mL. The MIC result reporting range for the VITEK 2 card is  $\leq 0.06 - \geq 8$  µg/ml.

**D. Type of Test:**

Automated quantitative or qualitative antifungal susceptibility test of *Candida* species to Micafungin

**E. Applicant:**

bioMérieux, Inc.

**F. Proprietary and Established Names:**

VITEK<sup>®</sup> 2 AST-Yeast Micafungin (0.06 - 8 µg/mL)

**G. Regulatory Information:**

1. Regulation section:

21 CFR 866.1640, Antimicrobial Susceptibility Test Powder

2. Classification:

II

3. Product code:

NGZ – Susceptibility Test Plate, Antifungal

LRG – Instrument for Auto Reader and Interpretation of Overnight Susceptibility Systems

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

83 Microbiology

**H. Intended Use:**

1. Intended use (s):

The VITEK<sup>®</sup> 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK<sup>®</sup> 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus spp.*, *Enterococcus spp.*, *Streptococcus spp.* and clinically significant yeast.

2. Indication(s) for use:

VITEK<sup>®</sup> 2 Yeast Micafungin is designed for antifungal susceptibility testing of *Candida* species. VITEK<sup>®</sup> 2 Yeast Micafungin is a quantitative test intended for use with the VITEK<sup>®</sup> 2 COMPACT Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK<sup>®</sup> 2 Yeast Micafungin has been shown to be active against most isolates of the microorganisms listed below, according to the FDA label for this antifungal.

Active *in vitro* and in clinical infections

*Candida albicans*  
*Candida glabrata*  
*Candida guilliermondii*  
*Candida krusei*  
*Candida parapsilosis*  
*Candida tropicalis*

The VITEK<sup>®</sup> 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK<sup>®</sup> 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus spp.*, *Enterococcus spp.*, *Streptococcus spp.*, *S. pneumoniae*, and clinically significant yeast.

3. Special conditions for use statement(s):

For prescription use only

The following limitations are included in the device labeling:

*“The ability of the AST card to detect resistance with the following combination(s) is unknown because an insufficient number of resistant strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory for further testing:*

*Micafungin: Candida glabrata”*

*“The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were not available at the time of comparative testing:*

*Micafungin: Candida spp”*

4. Special instrument requirements:

For use with the VITEK<sup>®</sup> 2 and VITEK<sup>®</sup> 2 Compact Systems

**I. Device Description:**

The VITEK<sup>®</sup> 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK<sup>®</sup> 2 test card contains 64 microwells. A control well containing only culture medium is included on all cards, with the remaining wells containing premeasured amounts of a specific antimicrobial agent in a culture medium base. A suspension of organism from a pure culture is prepared in a tube containing 0.45-0.5% sterile saline and standardized to a McFarland 0.5 using the DensiCHEK Plus™. The VITEK 2 System automatically fills, seals and places the card into the incubator/reader; manual methods can also be used for the inoculation of test cards for use in the VITEK 2 System. The VITEK 2 Compact has a manual filling, sealing and loading operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antimicrobial contained on the card.

The VITEK<sup>®</sup> 2 AST-Yeast Micafungin has the following concentrations in the card: 0.06, 0.25, 1 and 4 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK<sup>®</sup> 2 card is ≤0.06-≥8 µg/ml.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

VITEK<sup>®</sup> 2 AST-YST Flucytosine

2. Predicate 510(k) number(s):

K133952

3. Comparison with predicate:

<b>Similarities</b>		
<b>Item</b>	<b>Device VITEK 2 AST- Yeast Micafungin</b>	<b>Predicate VITEK 2 AST- YS Flucytosine (K133952)</b>
Intended Use	VITEK2 Yeast Micafungin is designed for antifungal susceptibility testing of Candida species. Vitek 2 Yeast Micafungin is a quantitative test intended for use with the VITEK 2 and VITEK 2 COMPACT Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents.	Same
Test Methodology	Automated yeast antifungal susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems (VITEK 2 Systems) to determine the in vitro susceptibility of Candida species.	Same
Inoculum	Saline suspension of organism	Same
Test Card	VITEK 2 Antifungal Susceptibility Test Card	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Analysis algorithm	Discriminate Analysis	Same

<b>Differences</b>		
<b>Item</b>	<b>Device</b>	<b>Predicate</b>
Antimicrobial Agent	Micafungin	Flucytosine
Antimicrobial Concentrations	0.06, 0.25, 1, 4	1, 4, 16, 32

**K. Standard/Guidance Document Referenced (if applicable):**

CLSI Document M27-A3, Reference Method for Broth Dilution Antifungal Susceptibility

#### **L. Test Principle:**

The VITEK<sup>®</sup> 2 System optics use visible light to directly measure organism growth. The transmittance optics are based on an initial light reading of a well before significant growth has begun. Periodic light transmittance samplings of the same well measure organism growth by how much light is prevented from going through the well. Several parameters based on the growth characteristics observed are used to provide appropriate input for the MIC calculations. Discriminate analysis is used to develop the algorithm that determines the susceptibility result for all antimicrobials on the VITEK<sup>®</sup> 2 System. The MIC result must be linked to organism identification in order to determine a category interpretation. A category interpretation (SIR) will be reported along with each MIC result.

#### **M. Performance Characteristics (if/when applicable):**

##### 1. Analytical performance:

###### *a. Precision/Reproducibility:*

Reproducibility studies included both the auto- and manual dilution methods with the VITEK 2 instrument system and the manual dilution method with the VITEK 2 Compact instrument system. With each inoculation method, the mode MIC was determined for each isolate and the reproducibility was calculated based on MIC values falling within  $\pm 1$  dilution of the mode MIC.

Testing using VITEK 2 and automatic dilution was performed using 10 *Candida* isolates (four isolates of *C. parapsilosis*, two *C. krusei*, two *C. norvegensis*, and two *C. guilliermondii*). Testing was done in triplicates at three clinical sites (two external sites and one internal site) on three separate days. All MIC values were on-scale and reproducibility demonstrated acceptable performance at 100%.

Initial studies using both the VITEK 2 and the VITEK 2 Compact and manual dilution did not meet acceptable reproducibility performance particularly due to *C. guilliermondii*. Per FDA's request, an additional study was performed using five isolates of *C. guilliermondii* with on-scale Micafungin MIC values. These isolates were tested in triplicate on three separate days at three sites and included a total of 45 data points at each site. The best and worst case reproducibility for VITEK 2 and VITEK 2 COMPACT using manual dilution were acceptable at 95.56% and 96.54%, respectively.

###### *b. Linearity/assay reportable range:*

Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Inoculum density control was monitored using the DensiCHEK Plus™ instrument. The DensiCHEK Plus™ was standardized weekly with all results recorded and in expected range.

A purity check of all organisms was performed at the time of VITEK 2 card inoculation. Only results obtained with pure cultures were evaluated.

Quality control testing was conducted throughout comparative testing at each site using two recommended quality control strains: *Candida krusei* (ATCC 6258) and *Candida parapsilosis* (ATCC 22019). In those instances where the test result was out-of-range for all replicates of the reference method, all data from that day’s testing was considered invalid and the testing for that day was repeated.

The QC organisms were tested a minimum of 20 times with the reference method, the VITEK 2 instrument platform (auto- and manual dilution methods), and with the VITEK 2 Compact instrument platform using the manual dilution method. QC results were interpreted after 24 hour of incubation. QC results for the VITEK 2 AST-Yeast Micafungin were within the expected results range  $\geq 99\%$  of the time for both instrument platforms and both dilution methods. A summary of the QC performance is provided in Tables 1 below.

**Table 1. Quality Control Results VITEK 2 Interpreted after 24 Hours of Incubation**

Organism	µg/mL	VITEK 2 Auto-Dilution		VITEK 2 Manual Dilution		VITEK 2 Compact Manual Dilution	
		Test	Ref.	Test	Ref.	Test	Ref.
<i>C. krusei</i> ATCC 6258	≤ 0.0313						
	0.0625						
	0.125	61	21	60	21	61	21
	0.25		39		39		39
	0.5		1		1		1
	1						
	2						
	4						
	8						
	16						
	32						
≥ 64							
<i>C. parapsilosis</i> ATCC 22019	≤ 0.0313						
	0.0625						
	0.125						
	0.25						
	0.5	61	28	61	28	61	28
	1		33		33		33

0.5-2µg/mL	2						
	4						
	8						
	16						
	32						
	≥ 64						

d. *Detection limit:*

Not applicable

e. *Analytical specificity:*

Not applicable

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

Results obtained with the bioMérieux VITEK2 AST-Yeast with Micafungin were compared to results obtained with the reference frozen broth microdilution panel. The VITEK2 AST Yeast Micafungin card contains the following concentrations: 0.25, 1, and 4 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC results range for the VITEK 2 card is ≤0.06 - ≥8µg/mL (eight dilutions). The frozen reference panel included a dilution range of 0.0156 - 32µg/mL (12 dilutions).

Test inocula were standardized using the DensiCHEK Plus instrument. VITEK 2 AST Yeast cards were inoculated using automatic dilution (for reading on the VITEK 2 instrument) or using a manual method (for reading on the VITEK 2 instrument or the VITEK2 COMPACT instrument. Reference panels were inoculated as outlined in CLSI M27-A3.

A total of 727 clinical isolates were evaluated at four sites (three external clinical sites and one internal clinical site) with VITEK 2 cards inoculated by automatic dilution and interpreted using the VITEK 2 instrument. The majority of the clinical isolates were fresh. Only 38 clinical isolates (5.2%) were stock isolates.

A total of 97 challenge isolates were tested at one site. The challenge set was tested with both of the card inoculation options, automatic and manual dilutions, on the VITEK 2 System and with the manual dilution on the VITEK 2 Compact System.

Results are summarized in Tables 2-3 below.

**Table 2. Overall Performance of Clinical and Challenge Isolates VITEK2 System, Automatic Dilution Method**

	EA TOT	EA <sup>a</sup> N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	# R	min	maj	vmj
<i>Clinical</i>	727	719	98.9	107	112	95.5	719	98.9	5	5	2	1
<i>Challenge</i>	97	96	99.0	17	16	94.1	77	79.4	1	20	0	0
<i>Combined</i>	824	815	98.9	129	123	95.3	796	96.6	6	25	2	1

<sup>a</sup>For antifungal agents, essential agreement is  $\pm$  two 2-fold serial dilutions

**EA** – Essential Agreement

**CA** – Category Agreement

**R** – resistant isolates

**maj** – major discrepancies

**vmj** – very major discrepancies

**min** – minor discrepancies

Essential agreement was calculated for when the VITEK 2 system results were within +/- two doubling dilutions of the reference method results. Category agreement was calculated for when the VITEK 2 system result interpretations agreed exactly with the reference method result interpretations. Evaluable results were defined as when both the reference method results and the VITEK 2 system results were on-scale.

Evaluable results were also defined as when the reference method results were on-scale and off-scale VITEK 2 system results clearly did not agree within the accepted +/- two doubling dilutions

**Table 3: Performance of Challenge Isolates Manual Dilution**

	EA TOT	EA <sup>a</sup> N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	# R	min	maj	vmj
VITEK 2 System	97	96	99.0	17	16	94.1	77	79.4	0	20	0	0
VITEK 2 Compact	97	96	99.0	17	16	94.11	77	79.4	0	20	0	0

<sup>a</sup>For antifungal agents, essential agreement is  $\pm$  two 2-fold serial dilutions

For challenge isolates tested with the VITEK 2 (auto and manual dilution) and the VITEK 2 Compact Systems inoculated using the manual dilution method (Tables 2-3), the overall CA is <90%. However, based on the AST Guidance, this was considered acceptable because all the categorical errors were minor and the data shows good EA of evaluable.

For clinical and challenge isolates of *Candida spp* for Micafungin using the VITEK 2 System, and the automatic dilution method (Table 2), the combined EA and CA met acceptance criteria of greater than or equal to 90%. However, there was one very major error in the clinical data of *C. glabrata*. The potential for occurrence of this error was mitigated by adding the following limitation in the labeling:

“The ability of the AST card to detect resistance with the following combination(s) is unknown because an insufficient number of resistant strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory for further testing”.

Micafungin: *Candida glabrata*

**MIC Trends:**

Using the data provided by the sponsor in the diagonal table format recommended in the AST Guidance, an analysis was conducted to check for trending in MIC values.

A higher reading trend was observed in the overall performance of *C. albicans* and *C. glabrata* compared to the CLSI broth micro-dilution method, which raises concerns for potential major errors as summarized in Table 6 below.

**Table 6. Higher Trending of Results in Combined Clinical and Challenge Study with *C. albicans* and *C. glabrata***

Organism	Difference in MIC as Compared to the CLSI Reference Method							Total
	≤-3	-2	-1	0	+1	+2	≥+3	
<i>C. albicans</i>	0	0	4% (19/482)	6.2% (30/482)	<b>47.09%</b> <b>(227/482)</b>	<b>42.1%</b> <b>(203/482)</b>	<b>0.6%</b> <b>(3/482)</b>	482
<i>C. glabrata</i>	0.5% (1/175)	0.5% (1/175)	12% (21/175)	17.7% (31/175)	<b>34.8%</b> <b>(61/175)</b>	<b>33.7%</b> <b>(59/175)</b>	0.5% (1/175)	175
<b>Total</b>	0% (1/657)	0% (1/657)	6% (40/657)	9.2% (61/657)	<b>43.8%</b> <b>(288/657)</b>	<b>39.9%</b> <b>(262/657)</b>	<b>0%</b> <b>(4/657)</b>	657

This trending and the potential for occurrence of major error(s) for Micafungin when testing *C. albicans* and *C. glabrata* with VITEK2 was addressed in the labeling by adding the following footnote under the interpretation table in labeling:

“VITEK<sup>®</sup>2 Micafungin MIC values for *C. albicans* and *C. glabrata* tended to be one or more doubling dilution higher compared to reference broth microdilution”.

A lower reading trend was observed in the overall performance of *C. krusei* and *C. parapsilosis* with both manual and automated inoculation methods compared to the CLSI broth micro-dilution method, which raises concerns for potential very major errors as summarized in Table 7 below.

**Table 7. Lower Trending of Results in Combined Clinical and Challenge Study with *C. krusei* and *C. parapsilosis***

Organism	Difference in MIC as Compared to the CLSI Reference Method							Total
	≤-3	-2	-1	0	+1	+2	≥+3	
<i>C. krusei</i>	0% (0/30)	0% (0/30)	<b>36.6%</b> <b>(11/30)</b>	46.6% (14/30)	13.3% (4/30)	3.3% (1/30)	0% (0/30)	30
<i>C. parapsilosis</i>	<b>3.6%</b> <b>(3/82)</b>	<b>2.4%</b> <b>(2/82)</b>	<b>39.0%</b> <b>(32/82)</b>	43.9% (36/82)	8.5% (7/82)	1.2%(1/82)	1.2% (1/82)	82
<b>Total</b>	<b>2.6%</b> <b>(3/112)</b>	<b>1.7%</b> <b>(2/112)</b>	<b>38.4%</b> <b>(43/112)</b>	44.6% (50/112)	9.8% (11/112)	1.7% (2/112)	0.9% (1/112)	112

This trending and the potential for occurrence of very major error(s) for Micafungin when testing *C. krusei* and *C. parapsilosis* was addressed by adding the following footnote in the labeling:

“VITEK<sup>®</sup> 2 Micafungin MIC values for *C. krusei* and *C. parapsilosis* organisms tended to be one doubling dilution lower compared to reference broth microdilution”.

Growth Rate:

All isolates tested during the clinical study grew using both the manual and the automatic dilution methods

*b. Matrix comparison:*

Not applicable

3. Clinical studies:

*a. Clinical Sensitivity:*

Not applicable

*b. Clinical specificity:*

Not applicable

*c. Other clinical supportive data (when a. and b. are not applicable):*

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

**Table 8. FDA Interpretive Criteria for Micafungin ( $\mu\text{g/mL}$ )**

Organisms	S	I	R
<i>C. albicans</i> <i>C. tropicalis</i> <i>C. krusei</i>	$\leq 0.25$	0.5	$\geq 1$
<i>C. parapsilosis</i> <i>C. guilliermondii</i>	$\leq 2$	4	$\geq 8$
<i>C. glabrata</i>	$\leq 0.06$	0.12	$\geq 0.25$

**N. Proposed Labeling:**

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

**O. Conclusion:**

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.