

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

K151817

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of caspofungin to the VITEK® 2 and VITEK® Compact Systems Antimicrobial Susceptibility Test (AST) Systems

C. Measurand:

The VITEK 2 AST Yeast card contains the following concentrations of caspofungin: 0.125, 0.5, 2, and 8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result reporting range for the card is 0.125 – 8 µg/mL.

D. Type of Test:

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

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK® 2 AST-YST Caspofungin ≤0.12 - ≥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® 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK® 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® 2 AST-YS Caspofungin is designed for antifungal susceptibility testing of *Candida* species and is 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. VITEK® 2 Yeast Caspofungin is a quantitative test. Caspofungin 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 clinical infections:

Candida albicans

Candida glabrata

Candida guilliermondii

Candida krusei

Candida parapsilosis

Candida tropicalis

The VITEK® 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK® 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.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

For use with the VITEK® 2 and VITEK® 2 Compact Systems

The following limitations are included in the device labeling:

“One non-susceptible isolate of C. glabrata gave a susceptible MIC result, a potential very major error.”

“The ability of VITEK 2 AST-YS to detect resistance to caspofungin is unknown because non-susceptible strains were not available for comparative testing. Isolates yielding caspofungin MIC results suggestive of a “non-susceptible” category (>2 µg/mL) should be submitted to a reference laboratory for further testing.”

I. Device Description:

The VITEK® 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK® 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.

VITEK 2 AST-YST Caspofungin has the following concentrations in the card: 0.125, 0.5, 2 and 8 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 AST-YST Caspofungin card is ≤ 0.12 - >8µg/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):
VITEK® 2 AST-YS Flucytosine
2. Predicate 510(k) number(s):
K133952
3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	Device	Predicate
	VITEK® 2 AST-YS Caspofungin	VITEK® 2 AST-YS Flucytosine (K133952)
Intended Use	Quantitative and qualitative susceptibility for colonies of <i>Candida spp.</i>	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 <i>in vitro</i> susceptibility of <i>Candida</i> species.	Same
Inoculum	Saline suspension of organism	Same
Test Card	VITEK 2 Test Card format	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same

Differences		
Item	Device	Predicate
	VITEK® 2 AST-YS Caspofungin	VITEK® 2 AST-YS Flucytosine (K133952)
Antimicrobial Agent	caspofungin	flucytosine
Antimicrobial Concentrations	Unique to caspofungin	Unique to flucytosine
Base broth	Unique to caspofungin	Unique to flucytosine
Analysis algorithms	Unique to caspofungin	Unique to flucytosine

K. Standard/Guidance Document Referenced:

CLSI Document CLSI M27-A3, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard - Third Edition

CLSI Document CLSI M27-S4, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Fourth Informational Supplement

L. Test Principle:

The VITEK® 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® 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:

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility studies were performed on the VITEK 2 and VITEK 2 Compact using both automatic dilution and manual dilution for panel inoculation. With each inoculation/reading methodology, the mode MIC was determined for each isolate and the reproducibility was calculated based on MIC values falling within ± 1 dilution of the mode MIC.

Testing using VITEK 2 and automatic dilution was performed at a total of four sites using 18 isolates representing species included in the intended use. Best case and worst case reproducibility for VITEK 2 with automatic dilution demonstrated acceptable performance at 96.7% and 95.3%, respectively.

Testing using VITEK 2 and manual dilution was performed using 10 *Candida* isolates tested at three sites. There were no off-scale results; best and worst case reproducibility was acceptable at 96.3%

Reproducibility studies were also performed using manual dilution and the Compact option using ten *Candida* strains tested at three sites. There were no off-scale results; best case and worst case reproducibility was acceptable at 98.9%.

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 and with VITEK 2 (manual and automatic dilution) and with the Compact option using manual dilution. QC results were interpreted after 24 hours of incubation. QC results for the VITEK 2 AST-YS Caspofungin were within the expected results range 100% of the time for both instrument platforms and both dilution methods. A summary of the QC performance is provided in Table 2 below.

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

QC Organism	Conc. ($\mu\text{g/mL}$)	VITEK 2 Automatic Dilution		VITEK 2 Manual Dilution		VITEK 2 Compact Manual Dilution	
		Test	Ref.	Test	Ref.	Test	Ref.
<i>C. krusei</i> ATCC 6258	0.015625						
	0.03125						
	0.0625						
	0.125	51		20		11	
	0.25	10	42	41	42	50	42
	0.5		19		19		19
	1						
	2						
	4						
	8						
≥16							
<i>C. parapsilosis</i> ATCC 22019	0.15625						
	0.03125						
	0.0625						
	0.125						
	0.25	1	1	1	1	1	1
	0.5	60	48	60	48	60	48
	1		12		12		12
	2						
	4						
	8						
≥16							

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-YS card with caspofungin were compared to results obtained with the reference frozen broth microdilution panel. The VITEK 2 AST-YS Caspofungin card contains the following concentrations: 0.125, 0.5, 2, and 8 µg/mL (Equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is 0.125 – 8 µg/mL. The frozen reference panel contained two-fold serial dilutions with a range of 0.0156 – 32 µg/mL.

Test inocula were standardized using the DensiCHEK Plus instrument. VITEK 2 AST-YS 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 VITEK 2 COMPACT instrument). Reference panels were inoculated as outlined in CLSI M27-A3.

A total of 755 clinical isolates were evaluated at three sites with VITEK 2 cards inoculated by automatic dilution and interpreted using the VITEK 2 instrument. The majority of isolates were fresh and recent isolates; 40 clinical isolates (5.3%) were stock isolates.

A total of 111 challenge isolates were tested at one site. The challenge set was tested with both of the card inoculation options, automatic dilution and manual dilution, on the VITEK 2 System and with the manual dilution on the VITEK 2 Compact System.

For isolates interpreted using the VITEK 2 System and inoculated using the automatic dilution option, the combined results from clinical and challenge testing demonstrated a combined EA of 99.7% and CA of 99.8% (Table 3). A total of 145 isolates were determined to be evaluable; the EA of evaluable isolates was determined to 98.6%. Two isolates of *C. glabrata* were determined to be non-susceptible by the reference method but susceptible by VITEK 2. Because the FDA Reference List Drug Label for caspofungin lists only a susceptible breakpoint (susceptible ≤ 2 µg/mL and non-susceptible > 2 µg/mL) these two isolates would be considered potential very major errors. Analysis of results from one of the two *C. glabrata* isolates indicated a contaminated culture; the sponsor chose not to remove results of this isolate from the performance determination; however, according to FDA's

current policy this isolate was not considered to be a potential very major error due to the technical error. The sponsor was asked to add the following limitation to the device labeling:

“One non-susceptible isolate of C. glabrata gave a susceptible MIC result, a potential very major error.”

For challenge isolates tested with the VITEK 2 System and inoculated using the manual dilution method, the results from challenge testing demonstrated an EA and CA of 100% (Table 4).

For challenge isolates tested with the VITEK 2 Compact System and inoculated using the manual dilution method, the results from challenge testing demonstrated an EA and CA of 100% (Table 5).

Because a limited number of non-susceptible isolates were evaluated, the sponsor was asked to include the following limitation in their device labeling:

“The ability of VITEK 2 AST-YS to detect resistance to caspofungin is unknown because non-susceptible strains were not available for comparative testing. Isolates yielding caspofungin MIC results suggestive of a “non-susceptible” category (>2 µg/mL) should be submitted to a reference laboratory for further testing.”

Table 3: Performance of Clinical and Challenge Isolates VITEK 2 System, Automatic Dilution Method

	Total	No. EA ^a	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min ^b	maj ^b	vmj ^b
Overall													
Clinical	755	752	99.6	119	117	98.3	753	99.7	2	755	N/A	N/A	N/A (2) ^c
Challenge	111	111	100.0	26	26	100.0	111	100.0	1	110	N/A	N/A	0
Combined	866	863	99.7	145	143	98.6	864	99.8	3	863	N/A	N/A	N/A (2)^c

^a For antifungal agents, essential agreement is ± two 2-fold dilutions

^b There are no intermediate or resistant interpretive criteria for caspofungin. The current absence of resistant isolates precludes defining any results other than “susceptible.”

^c These isolates are considered potential very major errors (a susceptible result obtained for an organism that tested non-susceptible by the reference method).

EA – Essential Agreement (+/- 2 dilutions)

CA – Category Agreement

EVAL – Evaluable isolates

NS – non-susceptible isolates

S – susceptible isolates

min – minor discrepancies

maj – major discrepancies

vmj – very major discrepancies

Table 4. Performance of Challenge Isolates, VITEK 2 Manual Dilution Method

	Total	No. EA ^a	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min ^b	maj ^b	vmj ^b
Overall													
Challenge	111	111	100.0	33	33	100.0	111	100.0	1	110	N/A	N/A	N/A

^a For antifungal agents, essential agreement is ± two 2-fold dilutions

^b There are no intermediate or resistant interpretive criteria for caspofungin. The current absence of resistant isolates precludes defining any results other than “susceptible.”

Table 5. Performance of Challenge Isolates, VITEK 2 Compact, Manual Dilution Method

	Tot	No. EA ^a	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min ^b	maj ^b	vmj ^b
Overall													
Challenge	111	111	100.0	32	32	100.0	111	100.0	1	110	N/A	N/A	N/A

^a For antifungal agents, essential agreement is \pm two 2-fold dilutions

^b There are no intermediate or resistant interpretive criteria for caspofungin. The current absence of resistant isolates precludes defining any results other than “susceptible.”

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 6. Susceptibility Interpretive Criteria

VITEK® 2 AST-YST	FDA Interpretive Categories* (MIC in µg/mL) Broth Microdilution MIC (mcg/mL) at 24 hours	
	<i>Candida sp.</i>	
Caspofungin	Susceptible	Non-Susceptible
	≤2	>2

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.