

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

A. 510(k) Number:

K133817

B. Purpose for Submission:

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

C. Measurand:

Fluconazole concentrations on VITEK 2 AST Yeast Fluconazole card: 2, 4,8,16, 32 and 64 µg/mL. The MIC result range for the card is $\leq 0.5 - \geq 64$ µg/mL.

D. Type of Test:

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

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK[®] 2 Yeast Fluconazole

VITEK[®] 2 AST-YS Fluconazole ($\leq 0.5 - \geq 64$ µg/mL)

G. Regulatory Information:

1. Regulation section:

866.1640, Antimicrobial Susceptibility Test Powder

2. Classification:

II

3. Product code:

NGZ – Susceptibility Test Plate, Antifungal

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 Yeast Fluconazole is designed for antifungal susceptibility testing of *Candida* species and 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 antifungal agents. VITEK[®] 2 Yeast Fluconazole 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 parapsilosis

Candida tropicalis

The following *in vitro* data are available, but their clinical significance is unknown.

Candida dubliniensis

Candida guilliermondii

Candida lusitanae

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.

Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):

- Fluconazole: *Candida glabrata*, *Candida kefyr*

4. Special instrument requirements:

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

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 antibiotic 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. 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 antibiotic contained on the card.

VITEK 2 AST-YST Fluconazole has the following concentrations in the card: 2, 4, 8, 16, 32 and 64 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 AST-YST Fluconazole card is ≤ 0.5 - ≥ 64.

The MIC interpretive criteria and equivalent concentrations are as follows:

VITEK® 2 AST-YST	Equivalent Standard Method Concentration by Efficacy in µg/mL	MIC Ranges and FDA Categories* (MIC in µg/mL)		
		S	I	R
Fluconazole	2, 4, 8, 16, 32, 64	<i>Candida spp.</i>		
		≤ 0.5 – 8	16 – 32	≥ 64

* FDA category interpretation indicated by boldface type

R = Resistant to usually achievable systemic concentrations.

I = Intermediate

S = Susceptible: Attainable levels in blood or tissue on usual usage, including oral administration when applicable.

J. Substantial Equivalence Information:

1. Predicate device name(s):

VITEK® 2 AST-YST Voriconazole

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

K092452

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	VITEK [®] 2 AST-YS Fluconazole	VITEK [®] 2 AST-YS Voriconazole (K092454)
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 in vitro 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 Fluconazole	VITEK [®] 2 AST-YS Voriconazole (K092454)
Antimicrobial Agent	Fluconazole	Voriconazole
Antimicrobial Concentrations	Unique to fluconazole	Unique to voriconazole
Analysis algorithms	Unique to fluconazole	Unique to voriconazole

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 using ten isolates (two isolates of *C. norvegensis*, two isolates of *C. krusei*, two isolates of *C. paraspilosis*, and one isolate each of *C. guilliermondii*, *C. lusitaniae*, *C. dubliniensis*, and *C. tropicalis*) in triplicate at three external clinical sites on three separate days. The 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. Greater than 95% reproducibility was demonstrated with both the VITEK® 2 and VITEK® 2 Compact Systems. A summary of the reproducibility study performance is provided in Table 1 below.

Table 1.

Instrument Platform	Inoculation Method	Best Case	Worst Case
VITEK® 2	Auto-Dilution	100%	100%
	Manual	100%	95.93%
VITEK® 2 Compact	Manual	100%	96.67%

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.

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 at 24 and 48 hour incubation times by the reference method, the VITEK 2 instrument platform using both auto- and manual dilution methods, and the VITEK 2 Compact instrument platform using the manual dilution method. QC results for the VITEK 2 AST-YS Fluconazole 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 2 and 3 below.

Table 2. Quality Control Results VITEK 2 (Compared to the expected QC ranges after 24 hours by the reference broth microdilution method)

Organism	Conc. ($\mu\text{g/mL}$)	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	≤ 0.25						
	0.5						
	1						
	2						
	4						
	8		39	1	39	1	38
	16	14	91	35	90	35	91
	32	109		93		93	
	64	7					
	≥ 128						
<i>C. parapsilosis</i> ATCC 22019	≤ 0.25						
	0.5		20		20		20
	1		104	7	103	9	104
	2	117	4	122	4	121	4
	4	12	2		2		2
	8	1					
	16						
	32						
	64						
	≥ 128						

Table 3. Quality Control Results VITEK 2 (Compared to the expected QC ranges after 48 hours by the reference broth microdilution method)

Organism	Conc. (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	≤ 0.25						
	0.5						
	1						
	2						
	4						
	8			1		1	
	16	14	3	35	3	35	3
	32	109	127	93	126	93	126
	64*	7					
	≥ 128						
<i>C. parapsilosis</i> ATCC 22019	≤ 0.25						
	0.5						
	1		66	7	65	9	66
	2	117	57	122	57	121	57
	4	12	7		7		7
	8	1					
	16						
	32						
	64						
	≥ 128						

*The result range of the VITEK 2 AST-YS Fluconazole (≤ 0.5 - ≥ 64 µg/mL) does not cover the entire expected CLSI/FDA QC range for 48 hour incubation reference method. All values ≥ 64 µg/mL were considered to be in QC. All *C. parapsilosis* results were within the acceptable range.

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:*

The performance of the VITEK 2 System was established for *Candida spp.* with a clinical study conducted at three external sites. Testing was done on 406 fresh clinical isolates and 85 challenge isolates in comparison to the 24 hour broth microdilution reference method as described in CLSI documents M27-A3 and M27-S4. Both automated and manual dilution methods were tested on the VITEK 2 System. Challenge isolates were also tested with the manual dilution method on the VITEK 2 Compact.

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. Results are summarized in Table 4 below.

Table 4.

Organism Group	Total Tested	# EA	% EA	Total Evaluable	# EA of Evaluable	% EA of Evaluable	# CA	% CA	# R	# vmaj	# maj	# min
Clinical Data												
<i>C.albicans</i>	174	165	94.8	16	12	75	167	96.0	2	0	2	5
<i>C.dubliniensis</i>	5	5	100.0	0	0	NA	5	100.0	0	0	0	0
<i>C.guilliermondii</i>	3	3	100.0	2	2	100.0	3	100.0	0	0	0	0
<i>C.haemulonii</i>	1	1	100.0	0	0	NA	1	100.0	0	0	0	0
<i>C.kefyr</i>	3	2	66.7	1	1	100.0	3	100.0	0	0	0	0
<i>C.lusitaniae</i>	23	21	91.3	6	5	83.3	21	91.3	1	0	0	2
<i>C.parapsilosis</i>	99	98	99.0	30	29	96.7	91	91.9	2	0	0	8
<i>C.pelliculosa</i>	2	2	100.0	2	2	100.0	2	100.0	0	0	0	0
<i>C.tropicalis</i>	94	89	94.7	31	28	90.3	86	91.5	2	0	0	8
<i>C.utilis</i>	2	2	100.0	2	2	100.0	2	100.0	0	0	0	0
Total	406	388	95.6	90	81	90	381	93.8	7	0	2	23
Challenge Auto-dilution Data												
<i>C.albicans</i>	41	41	100.0	3	3	100.0	40	97.6	2	0	0	1
<i>C.dubliniensis</i>	8	8	100.0	0	0	NA	8	100.0	0	0	0	0
<i>C.guilliermondii</i>	5	5	100.0	5	5	100.0	5	100.0	0	0	0	0
<i>C.lusitaniae</i>	5	5	100.0	2	2	100.0	5	100.0	0	0	0	0
<i>C.norvegensis</i>	1	1	100.0	1	1	100.0	1	100.0	0	0	0	0
<i>C.parapsilosis</i>	10	10	100.0	2	2	100.0	10	100.0	0	0	0	0
<i>C.pelliculosa</i>	2	2	100.0	2	2	100.0	2	100.0	0	0	0	0
<i>C.tropicalis</i>	13	12	92.3	6	6	100.0	11	84.6	0	0	0	2
Total	85	84	98.8	21	21	100.0	82	96.5	2	0	0	3
Challenge and Clinical Combined												
All Organisms	491	472	96.1	111	102	91.9	463	94.3	9	0	2	26

EA – Essential Agreement
CA – Category Agreement
R – resistant isolates

maj – major discrepancies
vmj – very major discrepancies
min – minor discrepancies

Clinical performance was acceptable. Due to performances obtained with *C. glabrata* and *C. kefyr*, the following limitation statement was added to the package insert:

“Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):

- Fluconazole: *C. glabrata*, *Candida kefyr*”

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:

VITEK [®] 2 AST-YST	Equivalent Standard Method Concentration by Efficacy in µg/mL	MIC Ranges and FDA Categories* (MIC in µg/mL)		
		S	I	R
Fluconazole	2, 4, 8, 16, 32, 64	<i>Candida spp.</i>		
		≤ 0.5 – 8	16 – 32	≥ 64

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.