

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

A. 510(k) Number:

K133952

B. Purpose for Submission:

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

C. Measurand:

Flucytosine concentrations on VITEK 2 AST Yeast Flucytosine card: 1, 4, 16, and 32 µg/mL. The MIC result range for the card is $\leq 1 - \geq 64$ µg/mL.

D. Type of Test:

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

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK[®] 2 Yeast Flucytosine

VITEK[®] 2 AST-YS Flucytosine ($\leq 1 - \geq 64$ 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* Flucytosine is designed for antimicrobial susceptibility testing of clinically significant yeast 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* Flucytosine is a quantitative test. Flucytosine 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

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

Candida dubliniensis

Candida guilliermondii

Candida lusitaniae

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

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, containing a premeasured amount of a specific antibiotic in a culture medium base. A control well, containing only culture medium, is included on all cards. 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.

The VITEK[®] 2 YS Flucytosine has the following concentrations in the card: 1, 4, 16, and 32 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK[®] 2 card is 1 - 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
Flucytosine	1, 4, 16, 32	<i>Candida spp.</i>		
		≤ 1 – 4	8 - 16	≥ 32

* 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 Flucytosine	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 Flucytosine	VITEK [®] 2 AST-YS Voriconazole (K092454)
Antimicrobial Agent	Flucytosine	Voriconazole
Antimicrobial Concentrations	Unique to flucytosine	Unique to voriconazole
Analysis algorithms	Unique to flucytosine	Unique to voriconazole

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

CLSI Document M27-A3, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Third Edition, Vol. 28 No.14

CLSI Document M27-S4, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Fourth Informational Supplement, Vol.32 No. 17

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 (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility studies were performed using ten isolates (four isolates of *C. krusei* and six isolates of *C. norvegensis*) 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%	100%
VITEK 2 [®] Compact	Manual	100%	100%

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 Flucytosine were within the expected results range $\geq 99\%$ of the time for both dilution methods. The MIC result range of the VITEK 2 AST-YS Flucytosine ($\leq 1 - \geq 64 \mu\text{g/mL}$) does not cover the expected CLSI/FDA QC range for *C. parapsilosis* for the 24 hour or 48 hour incubation reference method. All test instrument values $\leq 1 \mu\text{g/mL}$ for *C. parapsilosis* were considered to be in QC. 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	$\mu\text{g/mL}$	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 CLSI BMD Expected QC Range at 24 hours: 4 -16 $\mu\text{g/mL}$	≤ 0.0313						
	0.0625						
	0.125						
	0.25						
	0.5						
	1			1			
	2						
	4		6		6		6
	8	51	119	81	118	68	118
	16	77	3	45	3	59	3
	32						
	≥ 64						
<i>C. parapsilosis</i> ATCC 22019 CLSI BMD Expected QC Range at 24 hours: 0.06 – 0.25 $\mu\text{g/mL}$	≤ 0.0313						
	0.0625		42		41		42
	0.125		80		80		80
	0.25		6		6		6
	0.5						
	1*	128		127		128	
	2						
	4						
	8						
	16						
	32						
≥ 64							

* The minimum flucytosine concentration on the VITEK 2 AST-YST card is $1 \mu\text{g/mL}$.

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

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						
	0.25						
	0.5						
	1			1			
	2						
	4						
	8	53	47	83	47	70	46
	16	77	82	45	81	59	82
	32		1		1		1
	≥ 64						
<i>C. parapsilosis</i> ATCC 22019	≤ 0.0313						
	0.0625						
	0.125		10		10		10
	0.25		56		55		56
	0.5		64		64		64
	1*	130		129		130	
	2						
	4						
	8						
	16						
	32						
	≥ 64						

* The minimum flucytosine concentration on the VITEK 2 AST-YST card is 1 µg/mL.

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 AST YS Flucytosine was established for *Candida spp.* with a clinical study conducted at three external clinical sites. Testing was done on 557 fresh clinical isolates and 118 challenge isolates in comparison to the broth microdilution reference method incubated at 48 hours 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. Clinical performance was acceptable.

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>	176	173	98.3	5	4	80	173	98.3	7	0	0	3
<i>C.dubliniensis</i>	5	5	100	0	0	-	5	100	0	0	0	0
<i>C. glabrata</i>	148	147	99.3	0	0	-	147	99.3	5	0	0	1
<i>C.guilliermondii</i>	3	3	100	0	0	-	3	100	0	0	0	0
<i>C.haemulonii</i>	1	1	100	0	0	-	1	100	0	0	0	0
<i>C.kefyr</i>	4	4	100	0	0	-	4	100	0	0	0	0
<i>C.lusitaniae</i>	23	23	100	0	0	-	23	100	0	0	0	0
<i>C.parapsilosis</i>	99	98	99.0	0	0	-	98	99.0	1	0	0	1
<i>C.pelliculosa</i>	2	2	100	1	1	100	2	100	1	0	0	0
<i>C.tropicalis</i>	94	91	96.8	2	0	0	91	96.8	11	1*	0	2
<i>C.utilis</i>	2	2	100	0	0	-	2	100	0	0	0	0
Total	557	549	98.6	8	5	62.5	549	98.6	25	1*	0	7
Challenge Auto-dilution Data												
<i>C.albicans</i>	40	40	100	0	0	-	40	100	0	0	0	0
<i>C.dubliniensis</i>	8	8	100	0	0	-	8	100	0	0	0	0
<i>C. glabrata</i>	34	34	100	1	1	100	33	97.1	0	0	0	1
<i>C.guilliermondii</i>	5	5	100	0	0	-	5	100	0	0	0	0
<i>C.lusitaniae</i>	5	5	100	1	1	100	4	80.0	2	0	0	1
<i>C.norvegensis</i>	1	1	100	1	1	100	1	100	0	0	0	0
<i>C.parapsilosis</i>	10	10	100	0	0	-	10	100	0	0	0	0
<i>C.pelliculosa</i>	2	2	100	0	0	-	2	100	0	0	0	0
<i>C.tropicalis</i>	13	13	100	0	0	-	13	100	4	0	0	0
Total	118	118	100	3	3	100	116	98.3	6	0	0	2
Challenge and Clinical Combined												
All Organisms	675	667	98.8	11	8	72.7	665	98.5	31	1*	0	9

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

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

*The results of follow-up reference testing indicated that this isolate was 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:

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
Flucytosine	1, 4, 16, 32	<i>Candida spp.</i>		
		≤ 1 – 4	8 - 16	≥ 32

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