

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

A. 510(k) Number:

k112000

B. Purpose for Submission:

To obtain a substantial equivalence determination for this premarket notification for the addition of Penicillin to the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems for testing *Streptococcus* species.

C. Measurand:

Penicillin concentrations of 0.06, 0.125, 0.5, and 2 µg/mL

D. Type of Test:

The minimum inhibitory concentration (MIC) is determined using qualitative growth based detection algorithm using predetermined growth threshold. The MIC reporting result range of the card is $\leq 0.06 - \geq 8$ µg/mL.

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

VITEK[®] 2 Streptococcus Penicillin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645	Microbiology

H. Intended Use:

1. Intended use(s):

VITEK[®] 2 AST-ST Penicillin is designed for antimicrobial susceptibility testing of *Streptococcus* species. VITEK[®] 2 AST-ST Penicillin 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. Penicillin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

Active *in vitro* and in clinical infections
Beta hemolytic streptococci groups C and G
Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus viridans group
Streptococcus pneumoniae

2. Indication(s) for use:

VITEK[®] 2 AST-ST Penicillin is designed for antimicrobial susceptibility testing of *Streptococcus* species. VITEK[®] 2 Streptococcus AST-ST Penicillin 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. Penicillin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.

Active *in vitro* and in clinical infections
Beta hemolytic streptococci groups C and G
Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus viridans group
Streptococcus pneumoniae

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 essentially a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK 2 AST card contains 64 wells. A control well which only contains microbiological culture media is resident on all cards. The remaining wells contain premeasured portions of a specific antibiotic combined with culture media. The bacterial or yeast isolate to be tested is diluted to a standardized concentration with 0.45 – 0.5% saline before being used to rehydrate the antimicrobial medium within the card. 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 AST-ST Penicillin has the following concentrations in the card: 0.06, 0.125, 0.5, and 2 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is ≤ 0.06 – ≥ 8 µg/mL.

The MIC ranges, interpretive criteria and equivalent concentrations are as follows:

VITEK 2 AST-ST	Equivalent Standard Method Concentration by Efficacy in µg/mL	Organism	MIC Ranges and FDA/CLSI Categories MIC* in µg/mL:		
			S*	I	R
Penicillin	0.06, 0.125, 0.5, 2	<i>S. pneumoniae</i> (meningitis)	≤ 0.06	-	≥0.125
		<i>S. pneumoniae</i> (pneumoniae)	≤ 2	4	≥8
		Viridans Streptococci	0.125	0.25-2	≥4
		Beta hemolytic Streptococci**	0.125	-	-

* S = Susceptible; I = Intermediate; R = Resistant

**The current absence of resistant isolates precludes defining results other than susceptible. Isolates yielding results suggestive of non-susceptible should be submitted to a reference laboratory for further testing.

J. Substantial Equivalence Information:

1. Predicate device name(s):

VITEK 2 AST-GP Amoxicillin for *S. pneumoniae*

2. Predicate K number(s):

k063597

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Determining quantitative and qualitative susceptibility to antimicrobial agents	Same
Inoculation and test organism	Isolated colonies of <i>Streptococcus</i> species	Same
Instrument	Test are run on both the VITEK 2 and VITEK 2 Compact Systems	Same
Test Card	The VITEK 2 card, including base broth	Same
Test Method	Automated quantitative Antimicrobial susceptibility test to determine the <i>in vitro</i> susceptibility of <i>Streptococcus</i> species.	Same

Differences		
Item	Device	Predicate
Antibiotic	Penicillin-specific concentrations	Amoxicillin-specific concentrations
Reading algorithm	Unique to Penicillin	Unique to Amoxicillin

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

“Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071462.pdf>

Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard -8th Edition, Document M7-A8.

Performance Standards for Antimicrobial Susceptibility Testing – 19th Informational Supplement, M100-S19.

L. Test Principle:

Automated growth based detection using attenuation of light measured by an optical scanner. The optics used in the systems use visible light to directly measure organism growth. 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. The VITEK 2 System monitors the growth of each well in the card over a defined period of time. An interpretive call is made between 4 and 16 hours for a “rapid” read but may be extended to 18 hours in some instances. 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 on the card.

The VITEK 2 AST-ST Penicillin has the following concentrations in the card: 0.06, 0.125, 0.5, and 2 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 card is $\leq 0.06 - \geq 8$ µg/mL.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A reproducibility study was conducted at three external clinical sites. Ten *Streptococcus pneumoniae* isolates were tested at each site and testing was performed in triplicate over three days with the VITEK 2 AST-ST Penicillin card. Only *S. pneumoniae* isolates were used because of the difficulty in obtaining on-scale isolates with other *Streptococcus* species. The testing was performed using both the manual dilution method and the automated dilution mode. Testing was conducted on the VITEK 2 instrument.

For the sake of reproducibility calculations, off-scale values are handled in two ways; “best case” and “worst case” scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value.

The overall reproducibility was >95% with +/- one dilution observation for the VITEK 2 and the VITEK 2 Compact system. Only Manual Dilution testing was conducted since the VITEK 2 Compact system does not have a functionality to support automatic dilution to inoculate the card. Results were as follows:

VITEK System	Inoculation Method	Best Case	Worst Case
VITEK 2	AutoDilution	99.6%	99.6%
	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):*

The recommended *Streptococcus pneumonia* QC organism was tested on every test occasion with the reference method and the VITEK 2 System.

The reference method QC results were in range for every day tested. The VITEK 2 was tested a sufficient number of times to demonstrate that the system can produce QC results in the recommended range.

Quality Control was performed during the studies using both the auto-dilution and the manual method of diluting the organisms on the VITEK 2 System. Results demonstrated that methods were comparable.

Quality Control Results with the VITEK 2 System for Penicillin were as follows:

Organism	Concentration (µg/mL)	Auto Dilution		Manual Dilution	
		Reference	VITEK 2	Reference	VITEK 2
<i>Streptococcus pneumonia</i> ATCC 49619	0.06*				
	0.12*				
	0.25*	79	22	78	12
	0.5*	86	154	94	154
	1*	3	2	3	9
	2*				
	4*				
8*					
Acceptable MIC range: 0.25-1 µg/mL					

* VITEK Card Result Range is $\leq 0.06 - \geq 8$

At least one Quality control organism was in control in the reference on all days. Quality Control results for the VITEK 2 System using either inoculation dilution method demonstrated that the VITEK 2 System could produce the expected quality control results.

A similar QC study was conducted to evaluate the VITEK 2 Compact System. Results were compared to the expected FDA/CLSI QC results. With the

exception of one result, all 74 results for the VITEK 2 Compact System were within the expected QC range (98.6%).

Inoculum density control was monitored using the DensiChek2 instrument. This was standardized weekly with all results recorded and in the expected 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:

Performance was established through a clinical study which was conducted at four external study sites. A total of 1375 clinical isolates were tested by VITEK 2 AST-ST Penicillin with the VITEK® 2 System. The majority of the isolates were recently isolated from clinical specimens. Four hundred fifty seven of the 1375 clinical isolates tested were stock isolates (33.3%). The total number of viable clinical isolates evaluated was 1366. A challenge set consisting of 208 isolates was also evaluated with VITEK 2 AST-ST Penicillin. Testing of clinical isolates was performed using the automated method of inoculation and the challenge organisms were tested with both the manual dilution and automatic dilution. Each isolate was tested by the VITEK 2 AST-ST Penicillin and the CLSI broth microdilution reference method. The inoculum was prepared with direct colony suspension. A comparison was provided to the reference method with the agreement shown in the following tables. Fifty (3.2%) minor errors were seen with no major or very major errors. No growth was observed in 9 isolates.

AutoDilution

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus</i> species												
CLINICAL	1366	1353	99.0	234	226	96.6	1321	96.7	9	0	0	45
CHALLENGE	208	207	99.5	78	77	98.7	203	97.6	6	0	0	5
COMBINED (CLINICAL AND CHALLENGE)	1574	1560	99.1	312	303	97.1	1524	96.8	15	0	0	50

EA-Essential Agreement **CA**-Category Agreement **maj**-major discrepancies
vmj-very major discrepancies **min**-minor discrepancies

Because two separate breakpoints exist for penicillin when testing *Streptococcus pneumoniae* depending on the infection source, data was analyzed to evaluate performance based on the pneumonia and meningitis breakpoints separately as shown in the tables below. For the pneumonia breakpoint, 27 (7.7%) minor categorical errors were seen with no major errors. Of 350 total isolates of *S. pneumoniae*, none were considered resistant based on the penicillin breakpoint for pneumonia. Therefore, very major error rates could not be determined for *S. pneumoniae*.

AutoDilution (*S. pneumoniae*/pneumonia breakpoints)

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus pneumoniae</i> (pneumonia breakpoint)												
CLINICAL	300	293	97.7	116	110	94.8	276	92.0	0	0	0	24
CHALLENGE	50	49	98.0	49	48	98.0	47	94.0	0	0	0	3
COMBINED (CLINICAL AND CHALLENGE)	350	342	97.7	165	158	95.8	323	92.3	0	0	0	27

For the meningitis breakpoints, 6 (3.2%) major and 2 (1.2%) very major errors were observed. No minor errors were calculated due to the absence of an intermediate category.

AutoDilution (*S. pneumoniae*/meningitis breakpoints)

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus pneumoniae</i> (meningitis breakpoint)												
CLINICAL	300	293	97.7	116	110	94.8	292	97.3	112	2	6	na
CHALLENGE	50	49	98.0	49	48	98.0	50	100	49	0	0	na
COMBINED (CLINICAL AND CHALLENGE)	350	342	97.7	165	158	95.8	342	97.7	161	2	6	na

na= not applicable. No minor error calculation is made due to the absence of a defined intermediate category.

Essential agreement (EA) is when the VITEK 2 panels agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the VITEK 2 panel result interpretation agrees exactly with the reference panel result interpretation. Evaluable EA is when the MIC result is on scale for both the VITEK 2 and the reference and have on-scale EA.

The vast majority of evaluable results were based on *S. pneumoniae* and viridans streptococci. A high agreement was observed for combined Streptococci with a total EA of 99.1%, evaluable EA of 97.1% and a CA of 96.8%. Similarly, as shown in the above table, high agreement was observed for *S. pneumoniae* isolates based on the penicillin interpretive criteria for meningitis or pneumonia. This level of EA and CA is acceptable.

Because of the absence of an intermediate breakpoint, the results showed 6 (3.2%) major and 2 (1.2%) very major errors. This error rate was considered acceptable given the very high overall CA agreement and five were within EA and could have been minor errors if there was an intermediate category.

Performance of the VITEK® 2 and the VITEK® 2 Compact was also evaluated with the same 208 challenge organisms using the manual dilution method. A comparison was provided to the reference method with the following agreement as shown below.

Manual Dilution (VITEK 2)

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus species</i>												
CHALLENGE	208	207	99.5	78	77	98.7	203	97.6	6	0	0	5

Manual Dilution (VITEK 2 Compact)

Organism Group	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
<i>Streptococcus species</i>												
CHALLENGE	208	206	99.0	78	76	97.4	204	98.1	6	0	0	4

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:

According to the drug label provided by bioMerieux, the FDA interpretive criteria for penicillin for various *Streptococcus* species are as follows:

S. pneumoniae (meningitis): ≤ 0.06 (S), ≥ 0.125 (R) with no intermediate category

S. pneumoniae (pneumoniae): ≤ 2 (S), 4 (I), ≥ 8 (R)

Viridans species: ≤ 0.125 (S), 0.25-2 (I), ≥ 4 (R)

Beta hemolytic Streptococci: ≤ 0.125 (S) with no intermediate or resistant categories

N. Proposed Labeling:

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

O. Conclusion:

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