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

A. 510(k) Number:

k113783

B. Purpose for Submission:

Substantial equivalence determination for the addition of Penicillin to the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems for testing *Streptococcus pneumoniae*.

C. Measurand:

Penicillin concentrations of 0.06, 0.25, 1, 2 and 4 μg/mL. The MIC result range of the card is ≤ 0.06 – ≥ 8 μg/mL.

D. Type of Test:

The minimum inhibitory concentration (MIC) is determined using qualitative growth based detection algorithm according to a predetermined growth threshold.

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

VITEK® 2 AST – Gram Positive Penicillin for *Streptococcus pneumoniae*

G. Regulatory Information:

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

H. Intended Use:

1. Intended use:

   VITEK® 2 AST – Gram Positive Penicillin for *Streptococcus pneumoniae* is designed for antimicrobial susceptibility testing of *Streptococcus pneumoniae*. VITEK 2 AST – Gram Positive Penicillin for *Streptococcus pneumoniae* 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 microorganism listed below, according to the FDA label for this antimicrobial.

Streptococcus pneumoniae (pneumonia and meningitis)

2. Indication(s) for use:

VITEK® 2 AST – Gram Positive Penicillin for *Streptococcus pneumoniae* is designed for antimicrobial susceptibility testing of *Streptococcus pneumoniae*. VITEK 2 AST – Gram Positive Penicillin for *Streptococcus pneumoniae* 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 microorganism listed below, according to the FDA label for this antimicrobial.

Streptococcus pneumoniae (pneumonia and meningitis)

The VITEK® 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK® 2 and VITEK® 2 Compact 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 agalactiae*, and *S. pneumoniae*.

3. Special conditions for use statement:

For prescription use only.

The ability of the AST card to detect resistance to penicillin is unknown because resistant strains (based on the breakpoints for pneumonia) were not available at the time of comparative testing.

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 – GP Penicillin for *Streptococcus pneumoniae* has the following concentrations in the card: 0.06, 0.25, 1, 2 and 4 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 (Infection)	MIC Ranges and FDA/CLSI Categories MIC* in µg/mL:		
			S*	I	R
Penicillin	0.06, 0.25, 1, 2, 4	*S. pneumoniae* (meningitis)	≤ 0.06	-	≥0.125
		S. pneumoniae (pneumonia)	≤ 2	4	≥8

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

J. Substantial Equivalence Information:

1. Predicate device name:

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

2. Predicate K number:

   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 *Streptococcus*	Same

Similarities		
Item	Device	Predicate
	pneumoniae	
Instrument	Tests 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 *in vitro* susceptibility of *Streptococcus* pneumoniae	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

Clinical and Laboratory Standards Institute (CLSI) Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard -8th Edition, Document M7-A8.

CLSI Performance Standards for Antimicrobial Susceptibility Testing – Twenty-first Informational Supplement, M100-S21.

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 – GP Penicillin for *Streptococcus pneumoniae* has the following concentrations in the card: 0.06, 0.25, 1, 2 and 4µg/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.

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 – GP Penicillin for *Streptococcus pneumoniae* card. 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 assumes 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	100%	100%
	Manual	97.8%	97.8%
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 every day they were 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 and include data obtained from testing additional challenge isolates:

Organism	Concentration (µg/mL)	Auto Dilution		Manual Dilution	
		Reference	VITEK 2	Reference	VITEK 2
Streptococcus pneumonia ATCC 49619 Acceptable MIC range: 0.25-1 µg/mL	0.06*				1
	0.12*				
	0.25*	97	0	98	0
	0.5*	63	148	63	147
	1*	3	15	3	16
	2*				
	4*				
	8*				

* VITEK Card Result Range is ≤ 0.06 – ≥ 8.

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 and CLSI QC results.

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 three external study sites. A total of 500 clinical isolates were tested by VITEK® 2 AST – GP Penicillin for *Streptococcus pneumoniae* with the VITEK® 2 System. The majority of the isolates were recently isolated from clinical specimens. Two hundred forty seven of the 500 clinical isolates tested were stock isolates (49.4%). The total number of viable clinical isolates evaluated was 485; the no growth rate was 2.4% (15/500). A challenge set consisting of 50 isolates was also evaluated with VITEK® 2 AST – GP Penicillin for *Streptococcus pneumoniae* based on the pneumonia breakpoints. An additional 87 challenge isolates of *S. pneumoniae* were tested to further evaluate performance based on the meningitis breakpoint. 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 – GP Penicillin for *Streptococcus pneumoniae* 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.

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.

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
***Streptococcus pneumoniae* (pneumonia breakpoint)**												
CLINICAL	**485**	**472**	**97.3**	**171**	**162**	**94.7**	**448**	**92.4**	**2**	**0**	**1**	**36**
CHALLENGE	**50**	**50**	**100**	**49**	**49**	**100**	**46**	**92**	**1**	**0**	**0**	**4**
COMBINED (CLINICAL AND CHALLENGE)	**535**	**522**	**97.6**	**220**	**211**	**95.9**	**494**	**92.3**	**3**	**0**	**1**	**40**

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

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.

For the pneumonia breakpoint, 40 (7.5%) minor categorical errors were seen with one major error. A high agreement was observed with a total EA of 97.6%, evaluable EA of 95.9% and a CA of 92.3%. Of 535 total isolates of *S. pneumoniae*, three isolates were considered resistant based on the penicillin breakpoint for pneumonia but no very major errors occurred.

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
***Streptococcus pneumoniae* (meningitis breakpoint)**												
CLINICAL	**485**	**472**	**97.3**	**171**	**162**	**94.7**	**467**	**96.3**	**178**	**9**	**9**	**N/A**
CHALLENGE	**137**	**137**	**100**	**118**	**118**	**100**	**136**	**99.3**	**123**	**0**	**1**	**N/A**
COMBINED (CLINICAL AND CHALLENGE)	**622**	**609**	**97.9**	**289**	**280**	**96.9**	**603**	**96.9**	**301**	**9**	**10**	**N/A**

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

For the meningitis breakpoint, a high agreement was observed with a total EA of 97.9%, evaluable EA of 96.9% and a CA of 96.6%. In absence of an intermediate breakpoint for meningitis, the results showed 10 (3.1%) major and 9 (3.0%) very major errors. The major error rate of 3.1% was considered acceptable because of the high Category and Essential Agreements.

Performance of the VITEK® 2 and the VITEK® 2 Compact was also evaluated with the same 137 challenge organisms using the manual dilution method. A comparison to the reference is shown in the following tables:

Manual Dilution (VITEK 2)

Organism Group (breakpoint)	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	# vmj	# maj	# min
Streptococcus pneumoniae												
CHALLENGE (pneumonia)	**50**	**50**	**100**	**49**	**49**	**100**	**50**	**100**	**50**	**0**	**0**	**5**
CHALLENGE (meningitis)	**137**	**137**	**100**	**118**	**118**	**100**	**137**	**100**	**123**	**0**	**0**	**N/A**

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
Streptococcus pneumoniae												
CHALLENGE (pneumonia)	**50**	**50**	**100**	**49**	**49**	**100**	**50**	**100**	**50**	**0**	**0**	**4**
CHALLENGE (meningitis)	**137**	**137**	**100**	**119**	**119**	**100**	**137**	**100**	**123**	**0**	**0**	**N/A**

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:

S. pneumoniae (meningitis): ≤0.06 (S), ≥0.125 (R) with no intermediate category
S. pneumoniae (pneumoniae)**:** ≤2(S), 4 (I), ≥8 (R)

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.