510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K210287

B Applicant

bioMérieux, Inc

C Proprietary and Established Names

VITEK 2 AST- *Streptococcus* Cefotaxime (≤0.125 - ≥8 µg/mL).

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645 - Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System	MI - Microbiology
LTW	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LTT	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To update the VITEK 2 AST-*Streptococcus* Cefotaxime device labeling to include updated FDA-recognized breakpoints for *Streptococcus* spp Viridans Group, *Streptococcus pyogenes* (Group A ß-Hemolytic streptococci) and *Streptococcus* spp ß-Hemolytic Group (other than *S. pyogenes*) as published in the FDA STIC website.

Breakpoints for *Streptococcus pneumoniae* (meningitis) and (non-meningitis) (also indicated for use with this device) remain unchanged.

Previously obtained QC and reproducibility data is applicable to this reevaluation.

B Measurand:

Cefotaxime (≤0.125 - ≥8 µg/ml).

C Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test.

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

VITEK 2 AST-*Streptococcus* Cefotaxime is designed for antimicrobial susceptibility testing of *Streptococcus* spp. 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 AST-*Streptococcus* cefotaxime is a quantitative test.

Cefotaxime 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:

Streptococcus pneumoniae

Streptococcus pyogenes (Group A beta-hemolytic streptococci)*

Streptococcus spp. (Viridans group streptococci)

*The VITEK 2 *Streptococcus* susceptibility card also reports the susceptibility of the following additional organisms as listed on the FDA Susceptibility Test Interpretative Criteria web site (STIC): *Streptococcus* spp. ß-Hemolytic Group (other than *S. pyogenes*).

The VITEK 2 *Streptococcus* Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an in vitro test to determine the susceptibility of *S. pneumoniae*, beta-hemolytic *Streptococcus*, and Viridans *Streptococcus* to antimicrobial agents when used as instructed.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Limitation:
"*The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing:*
- *Cefotaxime (ctx01n): Streptococcus pyogenes (Group A ß-hemolytic streptococci) and Streptococcus spp ß-hemolytic Group (*other than *S. pyogenes*)".

D Special Instrument Requirements:

VITEK 2 and VITEK 2 COMPACT Systems.

IV Device/System Characteristics:

A 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 and sealing 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-*Streptococcus* Cefotaxime has the following concentrations in the card: 0.25, 0.5, 1, and 2 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. For all species, the MIC results range indicates that the VITEK 2 system is capable of producing the following MIC results ≤0.125, 0.25. 0.5, 1, 2, 4 and ≥ 8 µg/mL for AST-ST Cefotaxime test. This means the VITEK 2 systems does not provide results lower than 0.125 µg/mL, or greater than 8 µg/mL for the AST-ST Cefotaxime test.

B Principle of Operation:

The VITEK 2 and VITEK 2 Compact Systems utilize 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 within each of the 64 micro-wells. 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. At the completion of the incubation cycle, a report is automatically generated that contains the MIC value along with the interpretive category result for each antibiotic on the card.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Vitek 2 AST-ST Cefotaxime.

B Predicate 510(k) Number(s):

K121863

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device: K210287**	**Predicate: K121863**
Device Trade Name	Vitek 2 AST-*Streptococcus* Cefotaxime (≤0.125 -≥8 µg/mL)	Same
General Device Characteristic Similarities		
Intended Use/Indications for Use	VITEK 2 AST-*Streptococcus* Cefotaxime is designed for antimicrobial susceptibility testing of *Streptococcus* spp. 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. VITEK2 AST-*Streptococcus* Cefotaxime is a quantitative test.	Same
Test Method	Automated antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 COMPACT Systems to determine the in vitro susceptibility of microorganisms.	Same
Inoculum	Saline suspension of organism	Same
Test Card	*Streptococcus* (AST-ST) Susceptibility Card.	Same
Instrument	VITEK 2 and VITEK 2 COMPACT Systems	Same

Analysis Algorithm	Discriminate Analysis Algorithm	Same
Antimicrobial Concentrations & Result Range	Cefotaxime: for a calling range of ≤0.125, 0.25, 0.5, 1, 2, 4 ≥8 µg/mL.	Same
General Device Characteristic Differences		
FDA/CLSI Breakpoints	*Streptococcus spp Beta* Hemolytic *Group* ≤0.5(S), -, - *Streptococcus* spp. (Viridans Group): ≤1(S), 2(I), ≥4(R)	*Streptococcus spp:* *S. pyogenes (*Group A *ß*-Hemolytic streptococci*):* ≤0.5(S), 1(I), ≥2(R)
Indicated Organisms	Cefotaxime 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: *Streptococcus pneumoniae* *Streptococcus pyogenes* (Group A beta-hemolytic streptococci) *Streptococcus* spp (Viridans group streptococci The VITEK 2 *Streptococcus* susceptibility card also reports the susceptibility of the following additional organisms as listed on the FDA Susceptibility Test Interpretative Criteria web site (STIC): *Streptococcus* spp ß-Hemolytic Group (other than S. pyogenes). The VITEK 2 *Streptococcus* Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an in vitro test to determine the susceptibility of *S. pneumoniae*, *beta*-hemolytic *Streptococcus*, and Viridans *Streptococcus* to antimicrobial agents when used as instructed.	Cefotaxime 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: *Streptococcus pneumoniae* *Streptococcus pyogenes* (Group A beta-hemolytic streptococci) *Streptococcus* spp. 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 most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp, *Enterococcus* spp, *Streptococcus agalactiae*, and *S. pneumoniae*.

VI Standards/Guidance Documents Referenced:

Data that was reanalyzed to support this submission was previously obtained from a previously completed clinical studies. The clinical study was reviewed and cleared in K121863. The CLSI Standards listed below were effective during the original clearance:

- CLSI M7-A8, "*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically Approved Standard* –Eighth Edition" Vol. 29, No. 2 (January 2009).

- M100 S18., "Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. CLSI supplement

- *CLSI M100-S21, "Performance Standard for Antimicrobial Susceptibility Testing: Twenty-First Informational Supplement" Vol. 31, No. 1 (January 2011).*

- Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems, 2009.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Refer to K121863. Reproducibility testing for the VITEK 2 AST *Streptococcus* Cefotaxime was performed in support of clearance of K121863 and was determined acceptable.

2. Linearity:

   Not applicable.

3. Analytical Specificity/Interference:

   Not applicable.

4. Assay Reportable Range:

   Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Quality Control (QC) testing, Inoculum and Growth failure for the VITEK 2 AST *Streptococcus* Cefotaxime was performed in support of clearance of K121863 and was determined acceptable. QC testing specific to the changes in breakpoints was not performed in the current submission.

   The QC organism recommended by both the FDA and CLSI, namely *Streptococcus pneumoniae* ATCC 49619, was tested against Cefotaxime during the clinical study a

minimum 20 times/site by the VITEK 2 automatic and the manual dilution and the VITEK 2 Compact system using the manual dilution. The QC organism was tested by the VITEK 2 AST card and the reference broth microdilution method.

At the time of the original submission (K121863), the QC range for *S. pneumoniae* ATCC 49619 was 0.06-0.25µg/mL. The recommended CLSI QC range for this strain changed to include lower concentrations with a range of 0.03-0.12 µg/mL. However, the VITEK 2 MIC reporting range is ≤0.125 – ≥8 µg/mL. The VITEK 2 systems does not provide results lower than 0.125 µg/mL. Therefore, all QC results for *S. pneumoniae* ATCC 49619 are off scale for the VITEK 2 and VITEK 2 Compact Systems as both VITEK systems report the lowest end of the scale as ≤ 0.12 µg/mL. An MIC value of ≤0.12 µg/mL indicated that the quality control test results were acceptable (**Table 1**).

Table 1. Quality Control Results for VITEK 2 (Auto-Dilution and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Organism	VITEK 2 Result Range[1]	BMD Result Range (µg/mL)	VITEK 2 Auto-Dilution	BMD[2]	VITEK 2 Manual Dilution	BMD	VITEK 2 Compact Manual Dilution	BMD
		≤0.016		1		1		
		0.03						
		0.06		128		126		48
S. pneumoniae ATCC 49619	≤0.12	0.12	182	53	178	52	74	26
	0.5	0.5			1			
	1	1						
Expected Result: 0.03-0.12 µg/mL	2	2						
	4	4						
	≥8	8						
		16						
		≥32						

[1]VITEK 2 Card range is ≤0.125 - ≥8 and does not include the full CLSI/FDA recommended dilution range for QC testing with *S. pneumoniae*. The lowest dilution of the VITEK 2 Cefotaxime MIC range is ≤0.12 µg/mL. Obtaining this value was considered an indication that the quality control test results were acceptable.
[2]BMD: CLSI reference broth microdilution.

bioMérieux included the following as a footnote to the Quality Control table in the device labeling:

"*Does not include the full CLSI/FDA recommended dilution range for QC testing with this organism*".

The QC performance data is acceptable for the purpose of the re-evaluation of the performance of *Streptococcus spp.* when the new breakpoints are applied.

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The VITEK 2 AST-ST Cefotaxime ≤0.125 -≥8, which was originally cleared in K121863, included indications for *Streptococcus pneumoniae*, *Streptococcus* pyogenes (Group A beta-hemolytic streptococci) and *Streptococcus spp* tested with the VITEK 2 auto dilution and the VITEK 2 manual dilution and compared to the CLSI broth microdilution.

The performance of the VITEK 2 AST-ST Cefotaxime card with *Streptococococcus spp. (Viridans Group), Streptococcus pyogenes (Group A beta*-hemolytic streptococci*) and Streptococcus spp (*ß-hemolytic Group other than *S. pyogenes)* using revised interpretive criteria currently recognized by FDA was evaluated in the current submission using data obtained in support of K121863.

Since there was no change in the design or the dilution range of the VITEK 2 AST-ST card, the performance evaluation was achieved via re-analysis of the MIC data of the original 510(k) submission (K121863).

Even though the breakpoints for *Streptococcus pneumoniae* (meningitis) and (non-meningitis) did not change compared to the original submission, the performance of this organism as compared to the reference method was re-analyzed in the current submission.

A total of 1623 (clinical and challenge) *Streptococcus* spp. isolates were tested using the VITEK 2 with automatic dilution. The isolates included 1416 clinical isolates and 207 challenge isolates.

Results of the re-analyzed 1623 *Streptococcus* spp. clinical and challenge isolates (including 351 *Streptococcus pneumoniae*, 408 *Streptococcus* spp. Viridans Group, 310 *Streptococcus pyogenes* (Group A *ß*-hemolytic streptococci*) and 554 Streptococcus spp. ß*-hemolytic Group (other than *S. pyogenes*) are summarized in **Table 2.**

The previously collected data for the 207 challenge isolates tested at a single site with the VITEK 2 and the VITEK 2 Compact Systems using the manual dilution was also re-analyzed using the current breakpoints for *Streptococcus* spp Viridans Group, *S. pyogenes* (Group A beta-hemolytic streptococci) and *Streptococcus* spp. ß-Hemolytic Group (other than *S. pyogenes*). The results of the re-analysis are outlined in **Table 3.**

Table 2. Re-analysis of the Performance of *Streptococcus* spp for the Auto Dilution and the VITEK 2 AST-ST Cefotaxime.

	Total	#EA	%EA	Eval Total	No Eval EA	Eval EA %	#CA	%CA	No R/ NS	min	maj	vmj
***S. pneumoniae* (non-meningitis breakpoint) ≤1 (S), 2 (I), ≥4 (R)**												
Clinical	301	296	98.3	84	79	94.0	270	89.7	6	0	1	30
Challenge	50	50	100.0	35	35	100.0	45	90.0	17	0	0	5
Combined	351	346	**98.6**	119	114	95.8	315	**89.7**	23	35	1	0
***S. pneumoniae (meningitis breakpoints)* ≤0.5 (S), 1(I), ≥2 (R)**												

Clinical	301	296	98.3	84	79	94.0	270	89.7	29	29	2	0
Challenge	50	50	100.0	35	35	100.0	44	88.0	25	6	0	0
Combined	351	346	**98.6**	119	114	95.8	314	**89.5**	54	35	2	0
***S. pyogenes* (Group A ß-hemolytic streptococci) ≤0.5 (S), -, -**												
Clinical	260	260	100.0	0	0	0	260	100.0	0	NA	0	0
Challenge	50	50	100.0	0	0	0	50	100.0	0	NA	0	0
Combined	310	310	**100.0**	0	0	0	310	**100.0**	0	NA	0	0
***Streptococcus* spp (ß-hemolytic Group other than *S. pyogenes*) [a, b] ≤0.5(S), -, -**												
Clinical	497	497	100.0	0	0	0	497	100.0	0	NA	0	0
Challenge	57	57	100.0	0	0	0	57	100.0	0	NA	0	0
Combined	554	554	**100.0**	0	0	0	554	**100.0**	0	NA	0	0
***Streptococcus* spp Viridans Group[c] ≤1 (S), 2 (I), ≥4 (R)**												
Clinical	358	347	96.9	113	102	90.3	346	96.6	8	12	0	0
Challenge	50	50	100%	20	20	100%	50	100%	4	0	0	0
Combined	408	397	**97.3**	132	122	91.7	396	**97.1**	12	12	0	0

[a] Including the following tested species: *S. agalactiae, S. canis, S.dys.dysgalactiae, S.dys.equisimilis and S. equi zooepidemicus*.

[b] The interpretive criteria are applied to *Streptococcus* spp ß-Hemolytic Group according to the FDA STIC website.

[c] Including the following tested species: *S. anginosus, S. const. constellatus., S. constellatus. pharyngis, S. gordonii, S. intermedius, S. mitis, S. mitis/oralis, S. oralis, S. parasanguinis, S.sal.salivarius, S. sanguinis, S. alactolyticus, S. gal. gallolyticus, S. gal. pasteurianus.*

EA – Essential Agreement (+/- 2 dilutions)
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant
NS-Non-susceptible

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

Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of VITEK 2 test card within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the VITEK 2 test card and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the VITEK 2 test card.

When applying the new breakpoints of ≤1 (S), 2 (I), ≥4 (R) for *Streptococcus* spp. Viridans Group, the performance of the combined isolates tested with the VITEK 2 and automatic dilution is acceptable with 97.3% EA and 97.1% CA. There were no very major errors and no major errors. Twelve (12) minor errors out of 408 isolates (2.9%) tested were observed (**Table 2**).

When applying the new "susceptible only" breakpoints of ≤0.5 for *S. pyogenes* (Group A ß-hemolytic streptococci), the performance of combined isolates tested with the VITEK 2 and automatic dilution is acceptable with 100% EA and 100% CA. There were no very major errors and no major errors observed (**Table 2**).

When applying the new "susceptible only" breakpoints of ≤0.5 for *Streptococcus* spp (ß-hemolytic Group other than *S. pyogenes*), the performance of combined isolates tested with

the VITEK 2 and automatic dilution is acceptable with 100% EA and 100% CA. There were no very major errors and no major errors observed (**Table 2**).

Even though the breakpoints of *S. pneumoniae* (meningitis and non-meningitis breakpoints) did not change from the original submission (K121863), the performance of this organism was re-analyzed in the current submission to align with FDA current analysis of the evaluable results for Essential Agreement. For both, the non-meningitis and the meningitis breakpoints, no changes were observed in the %EA and the %CA and the performance remained acceptable. Applying the FDA current analysis resulted in a decreased percent evaluable EA for *S. pneumoniae* (non-meningitis and meningitis breakpoints) from 96.6% (in the original K121863 submission) to 95.8% in the current submission (**Table 2**).

Table 3. Re-analysis of the Performance of Streptococcus spp for the Manual Dilution with the VITEK 2 and the VITEK 2 Compact Systems AST-ST Cefotaxime.

VITEK 2 Systems	Total	#EA	%EA	Eval Total	No Eval EA	Eval EA %	#CA	%CA	No R/NS	min	maj	vmj
***S. pneumoniae* (Non-Meningitis breakpoint) ≤1(S), 2(I), ≥4(R)**												
VITEK 2	50	50	**100.0**	33	33	100.0	46	**92.0**	17	4	0	0
VITEK 2 Compact	50	50	**100.0**	34	34	100.0	44	**88.0**	17	6	0	0
***S. pneumoniae (meningitis breakpoints)* ≤0.5(S), 1(I), ≥2(R)**												
VITEK 2	50	50	**100.0**	35	35	100.0	44	**88.0**	25	6	0	0
VITEK 2 Compact	50	50	**100.0**	34	34	100.0	43	**86.0**	25	7	0	0
***S. pyogenes (Group A ß*-hemolytic streptococci) ≤0.5(S), -, -**												
VITEK 2	50	50	**100.0**	0	0	NA	50	**100.0**	0	NA	0	0
VITEK 2 Compact	50	49	**98.0**	1	0	0.00	49	**98.0**	0	NA	1	0
***Streptococcus* spp ß-Hemolytic Group (other than *S. pyogenes*) ≤0.5(S), -, -**												
VITEK2	57	57	**100.0**	0	0	0.00	57	**100.0**	0	NA	0	0
VITEK 2 Compact	57	57	**100.0**	0	0	0.00	57	**100.0**	0	NA	0	0
***Streptococcus* spp Viridans Group ≤1(S), 2(I), ≥4(R)**												
VITEK 2	50	50	**100.0**	20	20	100.0	49	**98.0**	4	1	0	0
VITEK 2 Compact	50	49	**98.0**	16	15	93.8	49	**98.0**	4	1	0	0

When applying the new breakpoints of ≤1 (S), 2 (I), ≥4 (R), the performance of *Streptococcus* spp (Viridans Group) challenge isolates tested with the manual dilution and the VITEK 2 and the VITEK 2 Compact systems is acceptable with % EA and % CA >90%. There were no very major errors, no major errors and only one minor error was observed with both the VITEK 2 and the VITEK 2 Compact out of 50 challenge isolates tested. (**Table 3**).

When applying the new "susceptible only" breakpoints of ≤0.5, the performance of *S. pyogenes* (Group A ß-hemolytic streptococci) challenge isolates tested with the manual dilution and the VITEK 2 and VITEK 2 Compact systems is acceptable with % EA and % CA >90%. There were no very major errors observed with the VITEK 2 and the VITEK 2 Compact. However, there was one major error out of 50 susceptible isolates (2%) observed with the VITEK 2 Compact. No major errors were observed with the VITEK 2 (**Table 3)**.

When applying the new "susceptible only" breakpoints of ≤0.5, the performance of *Streptococcus* spp (ß-hemolytic Group other than *S. pyogenes*) challenge isolates tested with the

manual dilution and the VITEK 2 and VITEK 2 Compact systems is acceptable with % EA and % CA >90%. There were no very major errors and no major errors observed. (**Table 3**).

For *S. pneumoniae* challenge isolates (non-meningitis and meningitis breakpoints) tested with the manual dilution and the VITEK 2 and VITEK 2 Compact systems, no changes were observed in the %EA, %CA and the % Evaluable EA compared to the original submission (K121863). The performance remained acceptable. (**Table 3**).

As required under 511A (2) (2) (B) of the Federal Food, Drug and Cosmetic Act, the following statement was included under Precautions Section in the device labeling:

Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.

Resistant Isolates Tested:
A total number of 12 *Streptococcus* spp. (Viridans Group) isolates out of 408 isolates tested (3%) provided resistant results with the revised breakpoints. The resistance has not drastically changed since the original clearance and the data set is still appropriate for evaluation with the new breakpoints. Based on the time of initial testing, the resistant strains evaluated in the original study likely represent the current resistance population.

Resistant strains of *S. pyogenes* (Group A ß-Hemolytic streptococci) and *Streptococcus* spp ß-Hemolytic Group were not available for testing in K121863.

bioMérieux included the following limitation in the device labeling:

"The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were either not available or an insufficient number were encountered at the time of comparative testing:

- *Cefotaxime (ctx01n): Streptococcus pyogenes (Group A ß-hemolytic streptococci) and Streptococcus spp ß-hemolytic Group (other than S. pyogenes)".*

Cefotaxime current interpretative criteria does not have intermediate or resistant interpretive criteria for *Streptococcus spp ß-Hemolytic Group (including S. pyogenes).*

bioMérieux also added the following footnote under the performance Table in the device labeling:

"NS-The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of NonSusceptible category should be submitted to a reference laboratory for further testing".

Trending

A trending re-analysis was performed using the combined (challenge and clinical) data obtained in K121863 from the VITEK 2 auto-dilution method for all *Streptococcus* spp to align with current trending analysis.

This trending calculation takes into account the MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered int the trending analysis.

When the difference between the percentage of isolates with higher vs. lower readings was greater than 30% and for which the confidence interval was determined to be statistically significant were considered to show evidence of trending. Trending that showed higher or lower MIC values compared to the reference is addressed in the labeling.

The evaluation of the MIC results for *Streptococcus* spp (Viridans Group) using auto dilution on the VITEK 2 instrument showed a trend toward lower MIC values when compared to the reference method (**Table 5**). No trending was observed with *Streptococcus pneumoniae* (meningitis and non-meningitis breakpoints), *Streptococcus* spp (beta-Hemolytic Group) and *S. pyogenes* (Group A beta-hemolytic streptococci) (**Table 5**).

Table 5. Trending Re-Analysis for *Streptococcus* spp with Cefotaxime and the VITEK 2 Automated Dilution

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)*	Trending Noted
Viridans Group	202	104	65	33	-35.1% (-43.3%, -26.2%)	Yes
S. pyogenes	0	NA	NA	NA	NA	NA
Streptococcus spp Beta-Hemolytic *Group (other than S. pyogenes)*	1	1	0	0	-100% (-100%, 12.21%)	No
S. pneumoniae-meningitis	132	22	60	50	21.2% (10.5%, 31.3%)	No
S. penumoniae-non meningitis	132	22	60	50	21.2% (10.5%, 31.3%)	No

*A positive percent difference value indicates higher MIC when compared to the reference method; A negative percent difference value indicates lower MIC when compared to the reference method.

To address the observed trending, bioMérieux included the following footnote to the performance table in the device labeling:

"*The VITEK 2 Cefotaxime MIC values for Streptococcus spp Viridans Group tended to be at least one doubling dilution lower than the reference method and may contribute to the occurrence of very major errors*".

2. Matrix Comparison:

Not Applicable

C Clinical Studies:

1. Clinical Sensitivity:

   Not Applicable

2. Clinical Specificity:

   Not Applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not Applicable

D Clinical Cut-Off:

Not Applicable.

E Expected Values/Reference Range:

The FDA recognized susceptibility interpretive criteria for Cefotaxime are listed in **Table 6**

Table 6: FDA Recognized Interpretative Criteria for Cefotaxime

Pathogen	Minimum Inhibitory Concentrations (µg/mL)[1]		
	S	I	R
S. pneumoniae (meningitis)	≤0.5	1	≥2
S. pneumoniae (non-meningitis)	≤1	2	≥4
Streptococcus spp Beta-Hemolytic Group[2]	≤0.5	-	-
Streptococcus spp Viridans Group	≤1	2	≥4

S = Susceptible; I = Intermediate; R = Resistant

[1] FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria Website https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

[2]Includes *S. pyogenes* (Group A beta-hemolytic streptococci) and other β-hemolytic streptococci other than *S. pyogenes*.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device when evaluated with the current FDA-recognized Cefotaxime breakpoints.

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate the VITEK 2 System with Cefotaxime when revised breakpoints for Cefotaxime are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, BioMérieux will update the Cefotaxime device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.