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

## I Background Information:

### A 510(k) Number

K251579

### B Applicant

bioMerieux, Inc.

### C Proprietary and Established Names

VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 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 |

## II Submission/Device Overview:

### A Purpose for Submission:

To obtain a substantial equivalence determination for the VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/ml), which was previously cleared in K222073, to expand the indications for use to include testing of additional Enterobacterales species with FDA STIC-recognized breakpoints and to include the VITEK COMPACT PRO instrument.

### B Measurand:

Cefazolin ≤1-≥32 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-Gram Negative Cefazolin is designed for antimicrobial susceptibility testing of Gram-negative bacilli and is intended for use with the VITEK 2 Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents.

VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) is a quantitative test. Testing is indicated for Enterobacterales (from infections other than uncomplicated UTI) as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC).

VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) has demonstrated acceptable performance with the following organisms:

Enterobacterales (*Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Klebsiella oxytoca, Citrobacter koseri*)

The VITEK 2 Gram Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram- negative bacilli to antimicrobial agents when used as instructed.

**C Special Conditions for Use Statement(s):**
Rx - For Prescription Use Only

Due to the occurrence of minor errors (resulting in a category agreement below 90% for the following species), perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination: Cefazolin (cz05n): *K. oxytoca* when the VITEK2 MIC is 8 µg/mL

The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were not available at the time of comparative testing: Cefazolin: *Citrobacter koseri*

**D Special Instrument Requirements:**

VITEK 2 Systems (i.e., VITEK 2, VITEK 2 Compact, and VITEK 2 Compact Pro), Software version 10.0 or newer

## 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 AST card contains 64 wells. A control well(s) which contain only nutrient medium is resident on all cards. The remaining wells contain premeasured portions of antimicrobials combined with the nutrient media. The isolate to be tested is diluted to a standardized concentration with 0.45 to 0.5% saline before being used to rehydrate the antimicrobial medium within the card.

VITEK 2 AST cards are intended to be used with VITEK 2 System instruments (VITEK 2, VITEK 2 Compact, and VITEK 2 Compact Pro). The VITEK 2 System is a fully automated instrument that integrates sample preparation, incubation, and optical measurement for microbial identification and antimicrobial susceptibility testing (AST).

The VITEK 2 instruments will automatically (or allow operator to manually) dilute the organism suspension to prepare an inoculum for susceptibility cards. Then, the VITEK 2 will fill, seal and place 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. The analysis program determines when a well demonstrates growth based on attenuation of light measured by an optical scanner. This data is used to determine the minimum inhibitory concentration or "MIC" values for the antimicrobial agent. 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-GN Cefazolin has the following concentrations in the card: 1, 2, and 8, µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 AST-GN Cefazolin card is ≤1-≥32 µg/mL.

### B Principle of Operation:

The VITEK 2 AST cards use an abbreviated doubling dilution series of antimicrobial to establish the MIC. Each VITEK 2 AST card contains 64 wells—one "growth" control well contains nutrient medium only, and the remaining wells contain premeasured antimicrobials in nutrient media.

The VITEK 2 System instruments (VITEK 2, VITEK 2 Compact, and VITEK 2 Compact Pro) utilize automated growth-based detection using attenuation of light measured by an optical scanner. The optics in the VITEK 2 Systems use visible light to directly measure organism growth in each well of the card over a defined period of time. Transmittance optics is based on an initial light reading of a well before significant growth has begun. Every 15 minutes throughout the incubation cycle (defined period of time based on the VITEK 2 card), light transmittance readings of each well determine organism growth by the amount of light that is prevented from passing through the well. At the completion of the incubation period, the MIC values and their associated interpretive category results for each antimicrobial on the test card are displayed in an automatically generated report.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):
VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL)

### B Predicate 510(k) Number(s):
K222073

### C Comparison with Predicate(s):

| Device & Predicate Device(s): | Device: K251579 | Predicate: K222073 |
|---|---|---|
| Device Trade Name | VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) | VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) |
| **General Device Characteristic Similarities** | | |
| Intended Use | VITEK 2 AST-Gram Negative Cefazolin is designed for antimicrobial susceptibility testing of Gram-negative bacilli and is intended for use with the VITEK 2 Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents.<br><br>VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) is a quantitative test. Testing is indicated for Enterobacterales (from infections other than uncomplicated UTI) as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC).<br><br>The VITEK 2 Gram Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed. | VITEK 2 AST-Gram Negative Cefazolin is designed for antimicrobial susceptibility testing of Gram-negative bacilli 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.<br><br>VITEK 2 AST-Gram Negative Cefazolin is a quantitative test.<br><br>The VITEK 2 Gram-Negative Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of clinically significant aerobic Gram-negative bacilli to antimicrobial agents when used as instructed. |
| Test Methodology | Automated identification and | Same |

| Device & Predicate Device(s): | Device: K251579 | Predicate: K222073 |
|---|---|---|
| | quantitative antimicrobial susceptibility test to determine the *in vitro* susceptibility of microorganisms. | |
| Inoculum | Saline suspension of organism | Same |
| Test Card | Gram Negative (AST- GN) Susceptibility Card | Same |
| Antimicrobial Agent | Cefazolin | Same |
| Concentrations of antimicrobial on card | 1, 2, 8 µg/ml | Same |
| Type of Test | Quantitative | Same |
| **General Device Characteristic Differences** | | |
| Instruments | VITEK 2, VITEK 2 Compact, and VITEK 2 Compact Pro Systems | VITEK 2 and VITEK 2 Compact Systems |
| Indications for Use | VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) has demonstrated acceptable performance with the following organisms:<br>Enterobacterales (*Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Klebsiella oxytoca, Citrobacter koseri*) | Cefazolin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial.<br><br>Active *in vitro* and in clinical infections**:**<br>*Escherichia coli, Proteus mirabilis* |

## VI Standards/Guidance Documents Referenced:

- Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.
- CLSI M07 11th Edition, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically (09/17/2018)
- CLSI M100 35th ed. Performance Standards for Antimicrobial Susceptibility Testing (January 2025)

## VII Performance Characteristics (if/when applicable):

## A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility of the VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) was previously assessed with species of Enterobacterales in K222073 and deemed acceptable. Refer to the K222073 Decision Summary for additional detail.

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):

   No new clinical data was provided as part of this submission. Quality Control (QC), inoculum density control, purity check, device failure, and growth failure rate for the for the VITEK 2 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) were previously assessed in K222073 and deemed acceptable. Refer to the K222073 Decision Summary for additional detail.

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

## B Comparison Studies:

1. Method Comparison with Predicate Device:

   Testing of cefazolin on the VITEK 2 AST-Gram Negative card was previously performed and reviewed as part of K222073. At the time of K222073 review, FDA STIC-recognized cefazolin breakpoints were restricted to *Escherichia coli* and *Proteus mirabilis,* and thus other species included in the clinical study were not included in analysis of performance. In this submission, the clinical data was re-analyzed to expand the indications for use to include all Enterobacterales species with STIC-recognized breakpoints.

Refer to the K222073 Decision Summary for complete details about the clinical study which remain identical with the exception of the total number or isolates, and organism included in this analysis.

Aa total of 862 isolates (713 clinical isolates and 149 challenge isolates) were evaluated using auto-dilution and VITEK 2 at four external sites (all within the US). Of these isolates, 63.4% (452/713) were recent isolates (tested within one year of isolation) and 36.6% (261/713) were stock isolates (no specific time from isolation). The clinical isolates included: 299 *Escherichia coli,* 45 *Proteus mirabilis,* 300 *Klebsiella pneumoniae,* 30 *Klebsiella, oxytoca*, 2 *Citrobacter koseri*, and isolates intrinsically resistant to cefazolin as described in CLSI M100 35th edition (30 *Klebsiella aerogenes*, 2 *Enterobacter cloacae complex*, 1 *Proteus vulgaris*, 1 *Providencia stuartii*, 1 *Serratia marcescens*, 1 *Citrobacter freundii*, and 1 *Morganella morganii*).

**Clinical and Challenge Data –VITEK 2 Auto-Dilution**
The results obtained using the auto-dilution method of the VITEK 2 from 862 total isolates are summarized in **Table 1**.

**Table 1. Performance of All Clinical and Challenge Isolates for Cefazolin: VITEK 2 Auto-Dilution**

| | Tot* | No. EA | EA % | Eval Tot | No. Eval EA | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Enterobacterales* [Breakpoints (µg/mL): ≤ 2(S), 4 (I), ≥8 (R)]** | | | | | | | | | | | | | |
| **Clinical** | 713 | 693 | 97.2 | 486 | 466 | 95.9 | 605 | 84.9 | 201 | 400 | 104 | 3 | 1 |
| **Challenge** | 149 | 147 | 98.7 | 69 | 67 | 97.1 | 143 | 96.0 | 98 | 14 | 6 | 0 | 0 |
| **Combined** | 862 | 840 | 97.5 | 555 | 533 | 96.0 | 748 | 86.8 | 299 | 414 | 110 | 3 | 1 |

***** Includes isolates of *E. coli, P. mirabilis, K. oxytoca, K. pneumoniae, and C. koseri.*

EA – Essential Agreement
CA – Category Agreement
Eval – Evaluable Isolates
R – Resistant
min – minor errors
maj – major errors
vmj – very major errors
S – Susceptible Isolates

Essential agreement (EA) occurs when the result of the reference method and that of the VITEK 2 AST-Gram Negative Cefazolin are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on- scale for both the reference method and the VITEK 2 AST-Gram Negative Cefazolin or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by the VITEK 2 AST-Gram Negative Cefazolin.

For all Enterobacterales organisms evaluated using the auto-dilution method of the VITEK 2, EA was acceptable at 97.5% (**Table 1**). The CA was 86.8% which was considered acceptable since most of the categorical errors were minor, the error rates for major errors (0.7%) and very major errors (0.3%) were acceptable, there was a high number of evaluable results, and the EA of evaluable results was good (96.0%).

When evaluating results by individual species, *Klebsiella oxytoca* had a CA <90% due to the occurrence of minor errors. Since the EA of the Evaluable was <90%, the following limitation statement was included in the device labeling:

*Due to the occurrence of minor errors (resulting in a category agreement below 90% for the following species), perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination: Cefazolin (cz05n): K. oxytoca when the VITEK2 MIC is 8 µg/mL*

*Citrobacter koseri* was evaluated by testing of cefazolin susceptible isolates only. Therefore, the following limitation was included in the device labeling.

*The ability of the AST card to detect resistance with the following combination(s) is unknown because resistant strains were not available at the time of comparative testing: Cefazolin: Citrobacter koseri*

**Challenge Data –VITEK 2 and VITEK 2 Compact Manul Dilution**

The 149 challenge isolates were also tested at one external site with the manual dilution option for the VITEK 2 and VITEK 2 Compact systems (summarized in **Table 2**).

**Table 2. Performance of Challenge Isolates for Cefazolin: VITEK 2 and VITEK 2 Compact Manual Dilution**

| | Tot* | No. EA | EA % | Eval Tot | No. Eval EA | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Enterobacterales* [Breakpoints (µg/mL): ≤ 2(S), 4 (I), ≥8 (R)]** | | | | | | | | | | | | | |
| **VITEK 2** | 149 | 146 | 98.0 | 68 | 65 | 95.6 | 140 | 94.0 | 98 | 14 | 9 | 0 | 0 |
| **VITEK 2 Compact** | 149 | 146 | 98.0 | 69 | 66 | 95.7 | 143 | 96.0 | 98 | 14 | 6 | 0 | 0 |

* Includes isolates of *E. coli, P. mirabilis, K. aerogenes, K. pneumoniae, and C. koseri.*

The overall performance of the VITEK 2 AST-Gram Negative Cefazolin when testing Enterobacterales with the manual dilution method is acceptable with an EA of 98.0%, a CA of 94.0%, and nine minor errors (6.0%).

The overall performance of the VITEK 2 AST-Gram Negative Cefazolin when testing Enterobacterales with the VITEK 2 Compact System is acceptable with an EA of 98.0%, a CA of 96.0%, and six minor errors (4.0%).

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included in the Precautions section of the device labeling to address testing and reporting of non-indicated species:

*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.*

**Trending**

A trending analysis was conducted using the combined data (clinical and challenge) obtained from the VITEK 2 auto-dilution method and VITEK 2 manual-dilution method. This trending calculation analyzes device MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method. MIC values that were off-scale for both the reference and device were not considered in the trending analysis. Species for which the difference between the percentage of isolates with higher or lower MIC values was ≥ 30% with a statistically significant confidence interval were considered to have evidence of trending and is addressed in the labeling. The trending analysis results are summarized in **Table 3** & **Table 4**.

**Table 3. Trending Analysis for Enterobacterales with Cefazolin and VITEK 2 Auto-Dilution**

| Organism | Total Evaluable for Trending | ≥ 1 Dilution lower No. (%) | Exact No. (%) | ≥ 1 Dilution Higher No. (%) | Percent Difference (CI) | Trending Noted |
|---|---|---|---|---|---|---|
| *Escherichia coli* | 232 | 37 (16.0%) | 99 (42.7%) | 96 (41.4%) | 25.4% (17.0%, 33.0%) | No |
| *Proteus mirabilis* | 76 | 17 (22.4%) | 52 (68.4%) | 7 (9.2%) | -13.0% (-25.0%, -1.0%) | No |
| *Klebsiella oxytoca* | 16 | 0 (0.0%) | 4 (25.0%) | 12 (75.0%) | 75%, (44.0%, 90.0%) | Yes |
| *Klebsiella pneumoniae* | 248 | 19 (7.7%) | 156 (62.9%) | 73 (29.4%) | 22%, (15%, 28%) | No |
| *Citrobacter koseri* | 2 | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) | 0%, (-66%, 66%) | No |

**Table 4. Trending Analysis for Enterobacterales with Cefazolin and VITEK 2 Manual-Dilution**

| Organism | Total Evaluable for Trending | ≥ 1 Dilution lower No. (%) | Exact No. (%) | ≥ 1 Dilution Higher No. (%) | Percent Difference (95% CI) | Trending Noted |
|---|---|---|---|---|---|---|
| *Escherichia coli* | 29 | 9 (31.0%) | 18 (62.1%) | 2 (6.9%) | -24%, (-43%, -4%) | No |
| *Proteus mirabilis* | 33 | 6 (18.2%) | 27 (81.8%) | 2 (6.9%) | -18%, (-34%, -4%) | No |
| *Klebsiella oxytoca* | 0 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | NA | NA |
| *Klebsiella pneumoniae* | 8 | 5 (62.5%) | 3 (37.5%) | 0 (0.0%) | -62%, (-86%, -17%) | Yes |
| *Citrobacter koseri* | 0 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | NA | NA |

Analysis of trending indicated that MIC values for *Klebsiella oxytoca* tended to be at least one doubling dilution higher than the reference MIC values. To address the MIC trending, the following statement has been added as footnote to the AST performance table:

*VITEK 2 AST-Gram Negative Cefazolin MIC values tended to be in exact agreement or at least one doubling dilution higher when testing Klebsiella oxytoca by VITEK 2 auto-dilution method compared to the CLSI reference broth microdilution method.*

Analysis of trending indicated that MIC values for *Klebsiella pneumoniae* tended to be at least one doubling dilution lower than the reference MIC values when tested by VITEK 2 manual dilution method. To address the MIC trending, the following statement has been added as footnote to the AST performance table:

*VITEK 2 AST-Gram Negative Cefazolin MIC values tended to be in exact agreement or at least one doubling dilution lower when testing Klebsiella pneumoniae by VITEK2 manual-dilution method compared to the CLSI reference broth microdilution method.*

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:**

**Table5. FDA-Recognized Interpretative Criteria for Cefazolin**

| Organisms | Minimum Inhibitory Concentrations (µg/mL)[a] | | |
|---|---|---|---|
| | S | I | R |
| Enterobacterales[b] | ≤2 | 4 | ≥8 |

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

[a] based on FDA STIC recognition of CLSI M100 (edition 35)
[b] excluding uncomplicated UTI

## VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

## 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 Predetermined Change Control Plan (PCCP) for a breakpoint change protocol that was reviewed and accepted by FDA in K250274. 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 AST-Gram Negative Cefazolin (≤1-≥32 µg/mL) when revised breakpoints for Cefazolin 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 VITEK 2 AST-Gram Negative Cefazolin 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.