510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K232395

B Applicant

bioMérieux SA

C Proprietary and Established Names

ETEST Sulbactam/Durlobactam (SUD) (0.004/4-64/4 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for Sulbactam/Durlobactam at concentrations of 0.004/4-64/4 µg/mL for susceptibility testing of the following microorganisms: *Acinetobacter baumannii-calcoaceticus* complex.

B Measurand:

Sulbactam/Durlobactam 0.004/4-64/4 µg/mL

C Type of Test:

Quantitative Antimicrobial Susceptibility Test growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

ETEST is a manual, quantitative technique for determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-positive aerobic bacteria and fastidious bacteria. The system comprises a predefined antibiotic gradient which is used to determine the Minimum Inhibitory Concentration (MIC, in µg/mL) of different antimicrobial agents against microorganisms tested on agar media after overnight incubation.

Sulbactam/Durlobactam has been shown to be active against the Gram-negative aerobic microorganisms listed below according to the FDA label for this antimicrobial agent.

ETEST SUD can be used to determine the MIC of Sulbactam/Durlobactam against the following microorganisms:

Active both *in vitro* and in clinical infections:

• *Acinetobacter baumanii-calcoaceticus* complex

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Due to the occurrence of a very major error with Sulbactam-Durlobactam (1/43 resistant isolates), isolates of *Acinetobacter baumannii-calcoaceticus* complex that provide an MIC of 4 µg/mL should be retested by an alternate method, if critical to patient care.

D Special Instrument Requirements:

Manual reading only

IV Device/System Characteristics:

A Device Description:

ETEST is a thin, inert and non-porous plastic strip carrying the MIC reading scale in µg/mL on one side and a predefined antibiotic gradient on the other side.

The ETEST gradient technology is based on a combination of the concepts of dilution and diffusion principles for susceptibility testing.

The ETEST consists of a thin, inert, nonporous plastic strip that is used to determine the antimicrobial susceptibility of bacteria. One side of the strip carries the minimum inhibitory concentration (MIC) reading scale expressed in µg/mL. The other side of the strip contains a predefined continuous exponential gradient of antibiotic concentrations.

ETEST Sulbactam/Durlobactam contains a range of Sulbactam from 0.004 to 64 µg/mL and Durlobactam at a fixed concentration of 4 µg/mL.

B Principle of Operation:

When the ETEST strip is applied to an inoculated agar surface, the preformed antibiotic gradient immediately transfers into the agar matrix, then forming a stable, continuous and exponential gradient of antibiotic concentrations directly underneath the strip. Bacteria growth becomes visible during incubation, and a symmetrical inhibition ellipse centered along the strip appears. After incubation, the MIC value is read from the scale in terms of µg/mL at complete inhibition of bacterial growth, where the pointed end of the ellipse intersects the strip. Since ETEST generates MIC values which fall between two-fold dilutions for interpretation, the MIC value read must be recorded to the next two-fold dilution.

V Substantial Equivalence Information:

A Predicate Device Name(s):

ETEST Meropenem/Vaborbactam (MEV) (0.004/8-64/8 µg/mL)

B Predicate 510(k) Number(s):

K183031

C Comparison with Predicate(s):

Table 1: Predicate Comparison

Device & Predicate Device(s):	**Device K232395**	**Predicate K183031**
Device Trade Name	ETEST Sulbactam/Durlobactam (SUD) (0.004/4-64/4 µg/mL)	ETEST Meropenem/Vaborbactam (MEV) (0.004/8-64/8 µg/mL)
General Device Characteristic Similarities		
Intended Use	ETEST is a manual, quantitative technique for the determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-positive aerobic bacteria and fastidious bacteria. The system comprises a predefined antibiotic gradient which is used to determine the Minimum	Same

Device & Predicate Device(s):	Device K232395	Predicate K183031
	Inhibito1y Concentration (MIC, in µg/mL) of different antimicrobial agents against microorganisms tested on agar media after overnight incubation.	
Test Design	Predefined exponential gradient of the dried and stabilized antibiotic covers a continuous concentration range across 15 two-fold dilutions of a conventional MIC method	Same
Inoculation	Isolated colonies from culture in a suspension equivalent to 0.5 McFarland. Inoculum is applied to agar with swab manually or with rotation plate for even distribution of inoculum.	Same
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip	Same
Results	MIC (µg/mL)	Same
General Device Characteristic Differences		
Antimicrobial Agent	Sulbactam/Durlobactam	Meropenem/Vaborbactam
Drug concentration Range	0.004/4-64/4 µg/mL	0.004/8-64/8 µg/mL
Indication for Use/Claimed Organisms	*Acinetobacter baumanii-calcoaceticus* complex	*Enterobacter cloacae* complex *Escherichia coli* *Klebsiella pneumoniae*
Incubation	35º±2º C for 20 – 24 hours	35º±2º C for 16 – 20 hours

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 33rd ed. *Performance Standards for Antimicrobial Susceptibility Testing* (March 2023)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites using 15 on-scale *Acinetobacter baumanii-calcoaceticus* complex isolates (10 *A. baumannii*, 3 *A. pittii* and 2 *A. nosocomialis*). Each isolate was tested in triplicate over three days for a total of 405 data points. The mode MIC value was determined for each isolate and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode. All MIC results were on scale. The testing resulted in overall reproducibility of greater than 95%. The results were acceptable.

2. Linearity:

   N/A

3. Analytical Specificity/Interference:

   N/A

4. Assay Reportable Range:

   N/A

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

   Inoculum Density Check:
   The inoculum was prepared to achieve turbidity equivalent to a 0.5 McFarland standard. Colony counts were performed periodically at each site for all QC replicates, from at least one replicate of each reproducibility isolate on each of the three days of testing, and from a minimum of 10% of the clinical and challenge strains tested. The inoculum densities were acceptable.

   Purity Check:
   Verification of isolate purity was conducted on all clinical, challenge, QC and reproducibility organism suspensions for each ETEST and from each growth control well of the broth microdilution reference panel. All organism suspensions for both the broth microdilution reference panels and ETEST were pure.

   Growth or Device Failure:

No device failures occurred in the ETEST Sulbactam-Durlobactam (SUD) (0.004/4-64/4 µg/mL) clinical trial.

Quality Control Testing:
One CLSI recommended QC strain (*A. baumannii* NCTC 13304) was tested at least 20 times per site at three sites using both ETEST and broth microdilution (BMD) reference methods. The results are summarized in Table 2.

The Quality Control results were within the recommended range > 95% of the time which is acceptable.

Table 2: Quality Control Test Results for ETEST Sulbactam-Durlobactam

QC Organism	Expected Range (SUD, µg/mL)	Concentration µg/mL*	Reference BMD (All Sites)	ETEST SUD (All Sites)
Acinetobacter baumannii NCTC 13304	0.5/4 – 2/4	<0.5		
		0.5	4	1
		1	84	112
		2	12	9
		>2	1	

*Durlobactam component of SUD was tested at a fixed concentration of 4 µg/mL.

6. Detection Limit:

   N/A

7. Assay Cut-Off:

   N/A

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Results obtained with ETEST Sulbactam-Durlobactam (SUD) (0.004/4-64/4 µg/mL) were compared to results obtained with the CLSI broth microdilution reference panel. The reference panel, prepared and interpreted according to recommendations outlined in the CLSI document M07 11th ed., contained two-fold serial dilutions of Sulbactam/Durlobactam with a concentration range of 0.004/4 – 64/4 µg/mL. At the end of incubation, the MIC value obtained from the ETEST (where the complete inhibition of growth intersects the strip) was compared to MIC results obtained with the reference method.

   The testing conditions for ETEST consisted of the following:
   - Inoculum: Direct colony suspension to achieve a suspension equivalent to a 0.5 McFarland standard suspension
   - Medium: Cation-adjusted Mueller Hinton agar

• Incubation: 35º±2º C for 20-24 hours

Clinical testing was performed at three external sites (Two US sites and one OUS site) and one internal site with both ETEST Sulbactam-Durlobactam and the reference method using a total of 461 *Acinetobacter-baumannii calcoaceticus* complex (*ABC* complex) (364 *A. baumannii*, 5 *A. calcoaceticus*, 1 *A. dijkshoorniae*, 65 *A. pittii*, 25 *A. nosocomialis* and 1 other *ABC* complex) clinical isolates. The clinical testing included 29.5% contemporary (136/461; isolated no longer than 6 months prior to testing) and 70.5% stock (325/461; no time limit on time from isolation prior to testing) clinical isolates. A total of 101 *ABC* complex (81 *A. baumannii*, 10 *A. pittii* and 10 *A. nosocomialis*) challenge isolates were also evaluated at one internal site using ETEST Sulbactam-Durlobactam and the reference method.

In total, the comparative study included clinical and challenge isolates as follows: 562 *ABC* complex isolates. They were: *A. baumannii* (445), *A. calcoaceticus* (5), *A. dijkshoorniae* (1), *A. pittii* (75), *A. nosocomialis* (35) and other *ABC* complex (1).

The performance of the 562 clinical and challenge isolates is summarized in Table 3.

Table 3: Performance of *Acinetobacter-baumannii calcoaceticus* complex (*ABC* complex)

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
***ABC* complex[a]**													
Clinical	461	450	97.6	433	422	97.5	453	98.3	31	424	7	0	1
Challenge	101	99	98.0	89	87	97.8	100	99.0	12	88	1	0	0
Combined	562	549	97.7	522	509	97.5	553	98.4	43	512	8	0	1

[a] *ABC* complex isolates included *A. baumannii*, *A. calcoaceticus*, *A. dijkshoorniae*, *A. pittii*, *A. nosocomialis* and other *ABC* complex.

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies
S – Susceptible

Essential Agreement (EA) is when the ETEST Sulbactam-Durlobactam results agree exactly or within one doubling dilution of the reference broth microdilution results. Category Agreement (CA) is when the ETEST Sulbactam-Durlobactam result interpretation agrees exactly with the reference broth microdilution result interpretation.

ETEST Sulbactam-Durlobactam performance for all *ABC* complex isolates (clinical and challenge) is acceptable with an EA of 97.7% and CA of 98.4%. There was no major error. One very major error was observed among 43 *ABC* complex resistant isolates (1/43 = 2.3%). This very major error was only due to an *A. baumannii* isolate. To mitigate the potential for occurrence of these errors, the sponsor included the following statement in the Limitation section of the device labeling:

Due to the occurrence of a very major error with Sulbactam-Durlobactam (1/43 resistant isolates), isolates of Acinetobacter baumannii-calcoaceticus complex that provide an MIC of 4 µg/mL should be retested by an alternate method, if critical to patient care.

Inoculator and ETEST Strip Applicator Options:
Culture media plates for ETEST can be inoculated and streaked by swabs manually or with the RETRO C80 inoculator. ETEST strips can be applied onto inoculated media using forceps, the NEMA C88 vacuum pen or the automatic Applicator SIMPLEX C76

The ETEST studies for Sulbactam-Durlobactam used manual inoculation with swabs and applied ETEST strips with forceps at all test sites. The following statement is included as a footnote to the performance table in the device labeling:

In the ETEST® Sulbactam/Durlobactam clinical studies, swabs were used for plate inoculation/streaking and forceps were used for ETEST® strip application. Testing with the optional Inoculator RETRO C80™, Vacuum Pen NEMA C88™, and Applicator SIMPLEX C76™ was not evaluated during the clinical studies.

MIC Trending Analysis
Using the combined clinical and challenge data, an analysis of trending was conducted for *Acinetobacter-baumannii calcoaceticus* complex. Results are stratified by species to determine if species-related trends were observed (Table 4). This trending calculation considers MIC values that are determined to be one or more doubling dilutions lower or higher compared to 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 in the trending analysis.

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

No significant trending was observed for *Acinetobacter-baumannii calcoaceticus* complex overall or for each individual species with ETEST Sulbactam-Durlobactam when compared to the reference method (Table 4).

Table 4. Trending Observed with ETEST Sulbactam-Durlobactam

	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)*	Trending Noted
Acinetobacter-baumannii calcoaceticus complex	525	108, (20.6)	301	116, (22.1)	2% , (-3%, 6%)	No

Resistance Mechanism Characterization
Challenge isolates of *Acinetobacter-baumannii calcoaceticus* complex harboring various molecular mechanisms of resistance noted in the FDA drug label were evaluated with ETEST Sulbactam-Durlobactam. Isolates with the following drug label listed mechanisms were evaluated: carbapenemase NDM, carbapenemase OXA, carbapenems impermeability.

2. Matrix Comparison:

N/A

C Clinical Studies:

1. Clinical Sensitivity:

N/A

2. Clinical Specificity:

N/A

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

N/A

D Clinical Cut-Off:

N/A

E Expected Values/Reference Range:

The FDA recognized susceptibility interpretive criteria for Sulbactam-Durlobactam are listed in Table 5.

Table 5. FDA Identified Interpretive Criteria for Sulbactam-Durlobactam

	Minimum Inhibitory Concentration (µg/mL)[a]		
Organisms	**S**	**I**	**R**
Acinetobacter-baumannii calcoaceticus complex	≤4/4	8/4	≥16/4

[a] FDA STIC Webpage https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

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 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 bioMérieux ETEST Sulbactam/Durlobactam (SUD) (0.004/4-64/4 µg/mL) when revised breakpoints for Sulbactam/Durlobactam 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 ETEST Sulbactam/Durlobactam 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.