510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K251580

B Applicant

Liofilchem s. r. l.

C Proprietary and Established Names

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

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 of the Liofilchem MIC Test Strip (MTS) containing sulbactam-durlobactam at concentrations of 0.004/4 – 64/4 µg/mL for susceptibility testing of *Acinetobacter baumannii calcoaceticus* complex.

B Measurand:

Sulbactam-durlobactam in the dilution range of 0.004/4 to 64/4 µg/mL

C Type of Test:

Quantitative antimicrobial susceptibility test (AST) growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The MTS (MIC Test Strip) Sulbactam-Durlobactam 0.004/4-64/4 µg/ml is a quantitative method intended for the in vitro determination of antimicrobial susceptibility of bacteria. MTS consists of specialized paper impregnated with a pre- defined concentration gradient of an antimicrobial agent, which is used to determine the minimum inhibitory concentration (MIC) in µg/ml of antimicrobial agents against bacteria as tested on agar media using overnight incubation and manual reading procedures. MTS Sulbactam- Durlobactam at concentrations of 0.004/4-64/4 µg/ml should be interpreted at 16-20 hours of incubation.

Testing with MTS Sulbactam-Durlobactam at concentrations of0.004/4-64/4 µg/mL is indicated for *Acinetobacter baumannii calcoaceticus* complex as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC).

The MTS Sulbactam-Durlobactam 0.004/4-64/4 µg/mL has demonstrated acceptable performance with the following organisms:

Acinetobacter baumannii calcoaceticus complex

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

N/A – Manual reading only

IV Device/System Characteristics:

A Device Description:

MTS Sulbactam-Durlobactam 0.004/4-64/4 µg/mL is made of special high-quality paper impregnated with durlobactam at a fixed concentration of 4 µg/mL and a predefined concentration gradient of sulbactam across 15 two-fold dilutions like those used by conventional MIC methods. One side of the strip is labeled with the sulbactam-durlobactam code (SUD) and the MIC reading scale in µg/mL. MIC values are determined by identifying the drug concentration at which growth of the ellipse ends. The MIC Test Strip (MTS) is single use only.

B Principle of Operation:

MTS are made of special high-quality paper impregnated with a predefined concentration gradient of antibiotic, across 15 two-fold dilutions like those of a conventional MIC method. When the MTS is applied onto an inoculated agar surface, the preformed exponential gradient of antimicrobial agent diffuses into the agar. After 16-20 hours incubation, a symmetrical inhibition ellipse centered along the strip is formed. The MIC is read manually directly from the scale in terms of µg/mL at the point where the edge of the inhibition ellipse intersects the strip MTS.

Growth along the entire gradient (i.e., no inhibition ellipse) indicates that the MIC value is greater than or equal to (≥) the highest value on the scale. An inhibition ellipse that intersects below the lower end of the scale is read as less than (<) the lowest value. An MIC of 0.125 µg/mL is considered to be the same as 0.12 µg/mL for reporting purposes.

An MTS MIC value which falls between standard two-fold dilutions must be rounded up to the next standard upper two-fold value before categorization.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Liofilchem MIC Test Strip (MTS)-Vancomycin 0.016 -256 ug/mL

B Predicate 510(k) Number(s):
K153687

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device: K251580**	**Predicate: K153687**
Device Trade Name	MTS Sulbactam-Durlobactam 0.004/4-64/4 µg/mL	Liofilchem MIC Test Strip (MTS)-Vancomycin 0.016 - 256 µg/mL
General Device Characteristic Similarities		
Plate Media	Mueller Hinton agar	Same
MTS Strip Material	High quality paper impregnated with a predefined concentration of gradient antimicrobial agent	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.	Same
Reading	Manual; Interpret the MIC as 100%	Same
Result	MIC in µg/mL MIC	Same
General Device Characteristic Differences		
Intended Use/ Indications For Use	Quantitative susceptibility to antimicrobial agents against specified gram-negative organisms	Quantitative susceptibility to antimicrobial agents against specified gram-negative organisms and gram-positive organisms
Antimicrobial Agent	Sulbactam-Durlobactam (SUD)	Vancomycin (VA)
Incubation	35°C ± 2°C for 16-20 hours	35°C ± 2°C for 24 hours

VI Standards/Guidance Documents Referenced:

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 28, 2009

CLSI M07-Ed12 "*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically.*"

CLSI M100-Ed34 "*Performance Standards for Antimicrobial Susceptibility Testing February 2024*"

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing of the Liofilchem MIC Test Strip (MTS) Sulbactam-Durlobactam was performed using 10 isolates of *Acinetobacter baumannii*. Testing was performed in triplicate at three sites on three separate days for a total of 270 data points (10 isolates x 3 replicates x 3 days of testing = 90 data points/site). Results were used to determine site to site and overall reproducibility.

   The mode MIC value was pre-determined for each organism and the reproducibility was calculated based on the number of MIC values that fell within ± one doubling dilution of the mode. All MIC results were on scale. The results for overall reproducibility of MTS Sulbactam-Durlobactam were 96.3% for all isolates of *Acinetobacter baumannii* that were within one doubling dilution of the mode MIC determined by the reference broth microdilution method. The results are 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):

   Inoculum Density Check:
   The inoculum is prepared from an overnight agar plate into saline to achieve turbidity equivalent to a 0.5 McFarland standard. The inoculum is applied to agar with a sterile swab manually or with a rotation plate. Colony counts are performed periodically at each site for all QC replicates.

Inoculum density checks were performed, and the colony counts obtained for the QC strain were within the recommended range of approximately 1 x 10^8 CFU/mL. Colony counts are also determined from one replicate of each reproducibility isolate on each of the three days of testing and from a minimum of 10% of the clinical strains tested and showed similar ranges.

Purity Checks:
Purity checks are performed on all isolates following MTS inoculation. All isolates were determined to be pure in both the broth microdilution reference panels and the MTS agar plates.

Growth Rate:
All clinical and challenge isolates grew in both the reference broth microdilution panels and the MTS agar plates.

Quality Control:
The QC strain recommended by the CLSI for routine QC testing of sulbactam-durlobactam (*Acinetobacter baumannii* NCTC 13304) was tested at three sites for a minimum of 20 times at each site by both the MTS and the reference method. The results demonstrate that MTS Sulbactam-Durlobactam can produce quality control results in the recommended range ≥95% of the time which is acceptable (**Table 2**).

Table 2. QC Results for Sulbactam-Durlobactam with CLSI Recommended QC Strains

QC Organism	Concentration (µg/mL)	Reference BMD (All Sites)	MTS (All Sites)
Acinetobacter baumannii NCTC 13304 Expected Results: 0.5/4-2/4 µg/mL	0.25		
	0.5		
	1	**97**	**64**
	2	**19**	**63**
	4		

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Results obtained with Liofilchem MTS with Sulbactam-Durlobactam were compared to results obtained from frozen reference MIC panels. Reference MIC panels are prepared, tested, and interpreted as outlined in the CLSI document M07-Ed12.

Isolated colonies from an overnight agar plate were suspended in saline to achieve a 0.5 McFarland standard turbidity (approximately 10^8 CFU/mL). Testing conditions consisted of incubation of the inoculated Mueller Hinton agar plate in an inverted position at 35°C ±2°C for 16-20 hours. At the end of the appropriate incubation, the MIC value where the edge of the inhibition ellipse intersects the strip was compared to MIC results obtained with the CLSI reference broth microdilution method.

Clinical:
Clinical testing was performed at two external U.S. sites and one internal outside U.S. site with both MTS Sulbactam-Durlobactam and the reference method. A total of 510 clinical isolates of *A. baumannii* were evaluated. The clinical testing included 379 (74.3%) contemporary isolates (isolated no longer than 6 months prior to testing) and 131 (25.6%) stock isolates (isolated over 6 months prior to testing).

Challenge:
Challenge testing was performed at one external U.S. site. A total of 78 challenge isolates of *A. baumannii* were evaluated.

Results of MTS Sulbactam-Durlobactam testing with clinical and challenge isolates are shown in **Table 3**.

Table 3. Overall Performance of MTS Sulbactam-Durlobactam with Clinical and Challenge Isolates

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	major	vmj
***Acinetobacter baumannii/calcoaceticus* complex, [≤4/4 (S), 8/4 (I), ≥16/4 (R)]**													
Clinical	510	495	97.1	501	486	97.0	477	93.5	13	488	31	2	0
Challenge	78	77	98.7	48	47	97.9	68	87.2	36	35	10	0	0
Total	588	572	97.3	549	533	97.1	545	92.7	49	523	41	2	0

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable MIC results
S – Susceptible
min – Minor discrepancies
maj – Major discrepancies
vmj – Very major discrepancies
R – Resistant

Essential Agreement (EA) is when the Liofilchem MIC Test Strip (MTS) results agree exactly or within one doubling dilution of the reference broth microdilution results. Category Agreement (CA) is when the Liofilchem MIC Test Strip (MTS) result interpretation agrees exactly with the reference broth microdilution result interpretation.

For *Acinetobacter baumannii-calcoaceticus* complex, the combined clinical and challenge results (588 isolates) were acceptable with an EA of 97.3% and CA of 92.7%. There were 41 minor errors, two (2) major errors (0.4%, 2/523) and no very major errors.

For clinical and challenge isolates tested with the Liofilchem MTS Sulbactam-Durlobactam, the overall % EA and % CA meet the acceptance criteria.

MIC Trending Analysis:
Using the combined clinical and challenge data, an analysis of trending was conducted for *Acinetobacter baumannii-calcoaceticus* complex (**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 MIC 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 statistically significant trending for with MTS Sulbactam-Durlobactam (0.004/4-64/4 µg/mL) was observed when compared to the CLSI broth micro-dilution reference method, as summarized in **Table 4**.

Table 4. Observed Trending of Results Obtained with MTS Sulbactam-Durlobactam

Organism Name	Total Evaluable for Trending	≥ 1 Dilution Lower No. (%)	Exact No.	≥ 1 Dilution Higher No. (%)	Percent Difference (95% CI)	Trending Noted
Acinetobacter baumannii/calcoaceticus complex	555	126, (22.7)	243	186, (33.51)	11%, (6%, 16%)	No

Resistant Isolates:
A total of 588 clinical and challenge isolates were tested for *Acinetobacter baumannii/calcoaceticus* complex and 49 (8.3%) resistant isolates were available for testing which is acceptable.

Testing/Reporting Non-Indicated Species:
For this review, the interpretative criteria are applied to the organisms/organism groups according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and Cosmetic Act, the following statement is added to the Precautions section of 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 labelling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

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:

Table 5. FDA-Recognized Interpretive Criteria for Sulbactam–durlobactam

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

[a]According to the FDA STIC Webpage

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.