510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K230479

B Applicant

Liofilchem s.r.l.

C Proprietary and Established Names

ComASP Cefiderocol 0.008-128

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY	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 obtain a substantial equivalence determination for Cefiderocol at concentrations of 0.008 – 128 µg/mL using a quantitative broth microdilution method

B Measurand:

Cefiderocol in the dilution range of 0.008 – 128 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 ComASP Cefiderocol 0.008-128 is a quantitative broth microdilution method intended for the in vitro determination of antimicrobial susceptibility of bacteria. ComASP Cefiderocol consists of polystyrene microtiter panels containing lyophilized concentrations of cefiderocol and tubes of media (iron-depleted cation adjusted Mueller Hinton broth), which are used to determine the minimum inhibitory concentration (MIC) in µg/mL using overnight incubation and manual reading procedures. ComASP Cefiderocol at concentrations of 0.008-128 µg/mL should be interpreted at 16-20 hours of incubation.

ComASP Cefiderocol can be used to determine the MIC of cefiderocol against the following microorganisms for which cefiderocol has been shown to be active clinically and *in vitro* according to the FDA drug approved label:

Acinetobacter baumannii complex

Escherichia coli

Enterobacter cloacae complex

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Manual reading only

IV Device/System Characteristics:

A Device Description:

Each ComASP Cefiderocol panel includes cefiderocol across 15 two-fold dilutions from 0.008 - 128 µg/mL and a positive control well in lyophilized form in two rows and the same well in the next two rows, allowing for testing of two bacterial isolates/panel. All wells are rehydrated with a standardized microbial suspension made in the iron-depleted cation-adjusted Mueller Hinton broth provided. After incubation for 16-20 hours the MIC result is read at the lowest concentration that completely inhibits growth.

ComASP Cefiderocol is supplied in a box of 4 cefiderocol panels which are individually packed in foil and each panel is configured to test 2 isolates at concentrations of 0.008-128 µg/mL. Also included are 8 tubes of iron-depleted cation-adjusted Mueller Hinton broth.

B Principle of Operation:

Each ComASP Cefiderocol panel includes cefiderocol across 15 two-fold dilutions from 0.008-128 µg/mL and a positive control well in lyophilized form in two rows and the same well in the next two rows, allowing for testing of two bacterial isolates/panel. All wells are rehydrated with a standardized microbial suspension made in the iron-depleted cation-adjusted Mueller Hinton broth provided. After incubation for 16-20 hours, the MIC result is manually read at the lowest concentration that completely inhibits growth.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Cefiderocol in the dilution range of 0.03-64 µg/ml

B Predicate 510(k) Number(s):
K203741

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device: K230479	Predicate: K203741
Device Trade Name	ComASP Cefiderocol 0.008-128	Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Cefiderocol in the dilution range of 0.03-64 µg/ml
General Device Characteristic Similarities		
Intended Use/Indications For Use	The ComASP Cefiderocol 0.008-128 is a quantitative broth microdilution	The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System is

Device & Predicate Device(s):	Device: K230479	Predicate: K203741
	method intended for the *in vitro* determination of antimicrobial susceptibility of bacteria. ComASP Cefiderocol consists of polystyrene microtiter panels containing lyophilized concentrations of cefiderocol and tubes of media (iron depleted cation adjusted Mueller Hinton broth), which are used to determine the minimum inhibitory concentration (MIC) in µg/mL using over overnight incubation and manual reading procedures. ComASP Cefiderocol at concentrations of 0.008-128 µg/mL should be interpreted at 16-20 hours of incubation. ComASP Cefiderocol can be used to determine the MIC of cefiderocol against the following microorganisms for which cefiderocol has been shown to be active clinically and *in vitro* according to the FDA drug approved label: *Acinetobacter baumannii* complex *Escherichia coli* *Enterobacter cloacae* complex *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Serratia marcescens*	an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious isolates This 510(k) is for Cefiderocol in the dilution range of 0.03-64 µg/mL for testing non-fastidious gram negative organisms on the Sensititre 18-24 hour MIC panel. Cefiderocol has been shown to be active both clinically and *in vitro* against the following organisms according to the FDA drug label: *Escherichia coli* *Enterobacter cloacae* complex *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Acinetobacter baumannii* *Serratia marcescens*
Antimicrobial Agent	Cefiderocol	Same
Test Panel	Microtiter plate with lyophilized drug	Same

Device & Predicate Device(s):	Device: K230479	Predicate: K203741
Indicated Organisms	*Acinetobacter baumannii* complex *Escherichia coli* *Enterobacter cloacae* complex *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Serratia marcescens*	Same
Result	MIC in µg/mL	Same
General Device Characteristic Differences		
Cefiderocol Concentration	0.008 – 128 µg/mL	0.03 – 64 µg/mL
Media	Iron-depleted cation-adjusted Mueller Hinton Broth	Cation-adjusted Mueller Hinton Broth with TES Buffer
Inoculation Method	Manual	Automated (AutoInoculator AIM) after preparation of a standard suspension
Incubation	35°C ± 2°C, 16-20 hours	34-36°C, 20-24 hours
Read Method	Manual	Automated on an ARIS/Autoreader/ OptiRead using fluorescence or on the Vizion by visual reading of growth.

VI Standards/Guidance Documents Referenced:

1. Food and Drug Administration, Center for Devices and Radiological Health. Guidance for Industry and FDA: Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems

2. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 32nd Ed. Approved standard, M100-S32, Clinical Laboratory and Standards Institute, Wayne, PA: CLSI; 2022.

3. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-11th Edition. CLSI document M07-A11. Wayne, PA: CLSI; 2018.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   A reproducibility study was performed at three sites using a panel comprised of 10 non-fastidious Gram negative organisms including three *P. aeruginosa*, two *A. baumannii* and five strains of Enterobacterales: (*K. pneumoniae* (two isolates), one *E. coli*, one *P. mirabilis* and one *S. marcescens*). All isolates were tested in triplicate over three days. The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. All MIC results were on scale. The testing resulted in overall reproducibility of greater than 95%. The results were 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):

   QC of Iron-Depleted Cation-Adjusted Mueller Hinton Broth used for Reference Panels
   QC of the reference panels with IMP-1 producing *P. aeruginosa* SR27001 were performed to verify proper chelation in production of panels. The target MIC of *P. aeruginosa* SR27001 is 2 µg/mL when the iron content of the iron-depleted cation-adjusted Mueller Hinton broth (ID-CAMHB) is acceptable (<0.03 mg/L) and a higher MIC indicates failure. The iron content of the reference panel lot was confirmed acceptable based on these parameters.

   QC of ComASP Cefiderocol 0.008-128 and Broth Microdilution Reference Method
   The QC isolates recommended by CLSI, namely *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested a sufficient number of times (i.e., at least 20/site) at each testing site using both ComASP and reference methods. The results are summarized in Table 1 below. The quality control results were in the expected range >95% of the time and are acceptable.

   Table 1. Cefiderocol ComASP QC Results

QC Organism	Cefiderocol Range (µg/mL)	Concentration (µg/mL)	Reference Frequency	ComASP Frequency
E. coli ATCC 25922	0.06-0.5	0.03	-	-
		0.06	5	
		0.12	18	35

QC Organism	Cefiderocol Range (µg/mL)	Concentration (µg/mL)	Reference Frequency	ComASP Frequency
		0.25	3	25
		0.5	-	3
		1	-	2
P. aeruginosa ATCC 27853	0.06-0.5	0.03	-	-
		0.06		8
		0.12	7	42
		0.25	16	10
		0.5	2	2
		1	-	-

Inoculum Density. Inoculum density checks were performed a sufficient number of times; all organism suspensions were in the acceptable range.

Purity Checks. Purity checks were performed for all testing of QC, reproducibility and clinical isolates. Only results from pure cultures were evaluated.

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Results obtained with ComASP Cefiderocol 0.008-128 were compared to results obtained from the reference method using frozen broth microdilution panels prepared according to CLSI document M7-A11. The reference MIC panels, including ID-CAMHB, were made strictly according to the CLSI procedures described in M7-A11, Appendix A and M100-Ed32 Appendix I. The components used for preparation of all reference MIC panels include cefiderocol which was prepared by Shionogi, calcium chloride, magnesium chloride, and zinc chloride (GFS Chemicals), Chelex 100 Resin (Bio-Rad), and BBL CAMHB powder (Becton Dickinson). Iron chelation was performed for 5 hours. Following addition of the cations, the iron content was assessed with Visocolor HE Iron (Macherey-Nagel) to confirm the iron content of the iron-depleted media did not exceed 0.03 mg/L in the final media. The iron content of the media was determined to be 0.02 mg/L.

Isolated colonies from blood agar plates incubated for 18-24 hours were suspended in saline to achieve a 0.5 McFarland standard turbidity (approximately 10^8 CFU/mL). The suspensions were inoculated into reference panel microtiter plates and incubated under ambient conditions at 35°C ± 2°C for 16-20 hours. Colony counts were performed to confirm the inoculum was in the acceptable range. At the end of the microtiter plate incubation, the MIC value was read at the

lowest drug concentration showing no growth (ignoring tiny button growth ≤1 mm, trailing or faint turbidity relative to the growth control) for all organisms.

Growth Rate:
The growth rate for the ComASP Cefiderocol 0.008-128 was 100%.

Clinical:
Clinical testing was performed at three sites (including one outside of the US). A total of 303 clinical isolates were tested which included 138 Enterobacterales isolates (30 *Klebsiella pneumoniae*, 33 *Escherichia coli*, 30 *Enterobacter cloacae*, 24 *Proteus mirabilis*, 21 *Serratia marcescens*), 90 *Pseudomonas aeruginosa*, and 75 *Acinetobacter baumannii* isolates. 61.7% of the clinical isolates were collected within 6 months of isolation.

Challenge:
Challenge testing was performed at one internal site. A total of 125 challenge isolates were tested which included 72 Enterobacterales isolates (20 *K. pneumoniae*, 22 *E. coli*, 12 *E. cloacae*, 10 *P. mirabilis*, 8 *S. marcescens*), 36 *P. aeruginosa* and 17 *A. baumannii* isolates.

The 428 clinical and challenge isolates are summarized in Table 2 below.

Table 2. Overall Performance of Clinical and Challenge Isolates

	Total	#EA	%EA	Eval EA Total	Eval EA #	Eval EA %	#CA	%CA	#R	#S	min	maj	vmj
Enterobacterales[a] ≤4 (S), 8 (I), ≥16 (R)													
Clinical	138	132	95.7	137	131	95.6	131	94.9	5	128	7	0	0
Challenge	72	69	95.8	63	60	95.2	63	87.5	25	37	9	0	0
Combined	210	201	**95.7**	200	191	95.5	194	**92.4**	30	165	16	0	0
***Pseudomonas aeruginosa* ≤1 (S), 2 (I), ≥4 (R)**													
Clinical	90	82	91.1	88	80	90.9	87	96.7	0	87	3	0	0
Challenge	36	36	100	35	35	100	29	80.6	16	15	7	0	0
Combined	126	118	**93.7**	123	115	93.5	116	**92.1**	16	102	10	0	0
***Acinetobacter baumannii* ≤1 (S), 2 (I), ≥4 (R)**													
Clinical	75	72	96.0	74	71	96.0	67	89.3	25	42	8	0	0
Challenge	17	17	100	12	12	100	17	100	14	3	0	0	0
Combined	92	89	**96.7**	86	83	96.5	84	**91.3**	39	45	8	0	0

[a] Including the following tested species: *K. pneumoniae* (50)*, E. coli* (55)*, E. cloacae* (42)*, S. marcescens* (29) and *P. mirabilis* (34).

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 ComASP Cefiderocol 0.008-128 results agree exactly or within one doubling dilution of the reference broth microdilution results. Category Agreement (CA) is when the ComASP Cefiderocol 0.008-128 result interpretation agrees exactly with the reference broth microdilution result interpretation.

The overall performance of all Enterobacterales isolates is acceptable with 95.7% EA and 92.4% CA. There were sixteen minor discrepancies and no major or very major errors.

The overall performance of *P. aeruginosa* is acceptable with 93.7% EA and 92.1% CA. There were ten minor errors and no major or very major errors.

The overall performance of *A. baumannii* is acceptable with 96.7% EA and 91.3% CA. There were eight minor errors and no major or very major errors.

Resistance Mechanisms

Challenge isolates of Enterobacterales, *P. aeruginosa*, and *A. baumannii* harboring various molecular mechanisms of resistance noted in the FDA drug label were tested with cefiderocol. Representative isolates harboring the following resistance mechanisms were evaluated: ESBLs (TEM, SHV, CTX-M, oxacillinase [OXA]), AmpC, AmpC-type ESBL (CMY), serine carbapenemases (such as KPC, OXA-48), and metallo-carbapenemases (such as NDM and VIM).

MIC Trends

A trending analysis was conducted using the combined data (clinical and challenge) obtained for each species. This trending calculation takes into account 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 in the trending analysis.

Organism groups 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 showed higher or lower MIC values compared to the reference is addressed in the labeling.

Table 3. Trending Analysis for Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* with Cefiderocol

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
Pseudomonas aeruginosa	124	44 (35.5)	34 (27.4)	46 (37.1)	2%	No
Acinetobacter baumannii	89	27 (30.3)	40 (44.9)	22 (24.7)	-6.0%	No
Escherichia coli	52	17 (32.7)	17 (32.7)	18 (34.6)	2.0%	No
Klebsiella pneumoniae	49	17 (34.7)	19 (38.8)	13 (26.5)	-8.0%	No
Enterobacter cloacae	42	18 (42.9)	16 (38.1)	8 (19.1)	-24.0%	No
Proteus mirabilis	32	8 (25.0)	6 (18.8)	18 (56.3)	31.0%	Yes (High)
Serratia marcescens	29	9 (31.0)	10 (34.5)	10 (34.5)	3%	No

Evaluation of ComASP Cefiderocol results showed trending toward higher MIC values for *P. mirabilis* (Table 3) when compared to the reference method. To address trending, the sponsor included the following footnote to the performance table:

Liofilchem ComASP Cefiderocol MIC values tended to be in exact agreement or at least one doubling dilution higher when testing P. mirabilis.

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-identified interpretative criteria for cefiderocol are listed in Table 4.

Table 4. FDA-Recognized Interpretative Criteria for Cefiderocol

	Minimum Inhibitory Concentrations (µg/mL)[a]		
Enterobacterales[b,c]	≤4	8	≥16
Pseudomonas aeruginosa	≤1	2	≥4
Acinetobacter baumannii complex	≤1	2	≥4

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

[b]Clinical efficacy was shown for *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae* complex in patients with complicated urinary tract infections (cUTI)

[c]Clinical efficacy was shown for *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* complex, and *Serratia marcescens* in patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)

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 Liofilchem intends to use to evaluate the Liofilchem ComASP Cefiderocol 0.008-128 with Cefiderocol when revised breakpoints for Cefiderocol are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Liofilchem will update the Cefiderocol 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.