510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K250885

B Applicant

Liofilchem Inc.

C Proprietary and Established Names

Ceftobiprole BPR 5 µg Disc

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JTN	Class II	21 CFR 866.1620 - Antimicrobial Susceptibility Test Disc	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

In this Traditional 510(k) submission, Liofilchem Inc. seeks the following:
1. Obtain a substantial equivalence determination for ceftobiprole antimicrobial susceptibility test disc.
2. Establish a Pre-Determined Change Control Plan (PCCP) to address future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage.

B Measurand:

Ceftobiprole 5 µg

C Type of Test:

Antimicrobial Susceptibility Test Disc

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Liofilchem Antibiotic Discs are a semi-quantitative agar diffusion method for *in vitro* determination of antimicrobial susceptibility of clinical isolates tested on agar media after overnight incubation.

The Ceftobiprole BPR 5 µg Disc is intended to determine susceptibility of Enterobacterales and *Staphylococcus aureus* to ceftobiprole, as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC). Ceftobiprole at concentrations of 5 µg should be interpreted at 16-18 hours of incubation.

The Ceftobiprole BPR 5 µg Disc demonstrated acceptable performance with the following organisms:

Enterobacterales (*Escherichia coli* and *Klebsiella pneumoniae*)
Staphylococcus aureus (includes methicillin resistant isolates)

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Due to the insufficient number of resistant *Staphylococcus aureus* isolates evaluated, the following limitation was included in the device labeling:

The ability of the Antibiotic Disc to detect resistance or non-susceptibility to antimicrobials as shown below is unknown because resistant strains were not available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.
Ceftobiprole: Staphylococcus aureus.

D Special Instrument Requirements:

Not applicable

IV Device/System Characteristics:

A Device Description:

The Liofilchem Ceftobiprole BPR 5 µg Disc is made of special high-quality paper impregnated with a predefined concentration of 5 µg of ceftobiprole. Both sides of the disc are labeled with "BPR 5", designating the agent and the drug content. Interpretive category results are determined by determining the inhibition zone diameter (mm) after incubation on an inoculated agar surface. The Liofilchem Ceftobiprole BPR 5 µg Disc is single use only.

B Principle of Operation:

Liofilchem Antibiotic Discs are made of specialized high-quality paper impregnated with a predefined concentration of an antimicrobial agent. The disc is removed from its packaging aseptically and applied to an inoculated agar surface, where the antimicrobial agent diffuses into the agar. After 16-20 hours incubation, the inhibition zone diameter is measured to the nearest millimeter with zone edges read at the point of complete inhibition. To categorize the result, the recognized zone size interpretive criteria for the antimicrobial agent being tested is used.

V Substantial Equivalence Information:

A Predicate Device Name(s):
BD BBL Sensi-Disc Cefiderocol 30ug (FDC-30)

B Predicate 510(k) Number(s):
K221826

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device: K250885**	**Predicate: K221826**
Device Trade Name	Ceftobiprole BPR 5 µg Disc	BD BBL Sensi-Disc Cefiderocol 30µg (FDC-30)
General Device Characteristic Similarities		
Test Method	Antimicrobial susceptibility testing using paper disks impregnated with an antimicrobial agent	Same
Plate Media	Mueller Hinton Agar	Same
Disc Material	High quality paper impregnated with a predefined concentration of antimicrobial agent	Same
Inoculation	Isolated colonies from a culture in a suspension equivalent to 0.5 McFarland. Inoculum is applied to agar with swab manually or with rotation plate.	Same
Reading Method	Measurement of inhibition zone diameter in mm	Same
Result Interpretation	Categorical interpretation (S/I/R) as determined by the measured zone diameters according to established interpretive criteria for the drug	Same

Device & Predicate Device(s):	Device: K250885	Predicate: K221826
General Device Characteristic Differences		
Intended Use/ Indications for Use	Semi-quantitative susceptibility to antimicrobial agents against specified gram-negative and gram-positive organisms	Semi-quantitative susceptibility to antimicrobial agents against specified gram-negative organisms
Antimicrobial Agent (Concentration)	Ceftobiprole (5µg)	Cefiderocol (30µg)

VI Standards/Guidance Documents Referenced:

- CLSI M100-35th ed. *Performance Standards for Antimicrobial Susceptibility Testing* (January 2025).
- CLSI M07-11th ed. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* (January 2018).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Reproducibility testing of the Liofilchem Ceftobiprole BPR 5 µg Disc was conducted at one internal site using 20 organisms, including 10 gram-negative organisms and 10 gram-positive organisms. Each isolate was tested in triplicate on three separate days across two disc lots using one lot of media (Mueller Hinton agar media). Each test was visually read by three independent readers with results blinded, resulting in 540 data points for evaluation (20 isolates x 3 replicates x 3 users x 3 days x 1 site x 1 media lot = 540 data points).

The reproducibility study included the following species: ten *Staphylococcus aureus* and ten Enterobacterales (4 *Enterobacter cloacae*, 4 *Escherichia coli*, and 2 *Klebsiella pneumoniae*).

Reproducibility was calculated as the percent of results which were within ±3 mm difference in zone diameter comparing test results with the modal zone diameter value. The reproducibility performance between disc lots and across readers was 100% and meets the acceptance criteria. Results are shown in **Table 1**.

Table 1: Reproducibility Summary for Ceftobiprole (5 µg) Disc

Between Disc Lots			Across Readers			
Lot #1	**Lot #2**	**All Lots**	**Reader #1**	**Reader #2**	**Reader #3**	**All Readers**
100% (270/270)	100% (270/270)	100% (540/540)	100% (180/180)	100% (180/180)	100% (180/180)	100% (540/540)

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:
The CLSI-recommended quality control (QC) isolates *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were tested using two Ceftobiprole BPR 5 µg Disc lots and at least 20 replicates per lot per reader. Each test was visually read by three independent readers, resulting in 240 disc data points. Results were compared to reference broth microdilution. The Liofilchem Ceftobiprole BPR 5 µg Disc QC performance was > 95% and is acceptable. The performance is summarized in **Table 2.**

Table 2: Quality Control Performance of Ceftobiprole BPR 5 µg Disc

QC Organism	Zone Diameter in millimeter (mm)		
	Range	Liofilchem Lot 1	Liofilchem Lot 2
Escherichia coli ATCC 25922 Expected Range: 25-31 mm	24		
	25		
	26	18	11
	27	22	28
	28	12	11
	29	8	7
	30		3
	31		
	32		
Staphylococcus aureus ATCC 25923 Expected Range: 20-27 mm	19		
	20		
	21		
	22	13	10
	23	27	27
	24	20	15
	25		8
	26		
	27		
	28		

ATCC=American Type Culture Collection

Broth micro dilution (BMD) for QC isolates was performed as per CLSI M07 on every day of clinical study to provide assurance of the data quality obtained from the reference method. The QC performance for the reference BMD method was acceptable at ≥95%. The performance is shown in **Table 3** below.

Table 3. Broth Microdilution Quality Control Summary for Ceftobiprole

QC Organism	MIC (µg/mL)	Reference Results
Escherichia coli ATCC 25922 Expected range: 0.03-0.12 µg/mL	≤0.016	
	0.032	13
	0.064	47
	0.125	
	≥0.25	
Staphylococcus aureus ATCC 29213 Expected range: 0.12-1 µg/mL	≤0.064	
	0.125	
	0.25	46
	0.5	14
	1	
	2	

ATCC=American Type Culture Collection

Inoculum Density Check:
Colony counts were conducted for all QC and reproducibility isolates, as well as 10% of clinical isolates. All counts were within the expected range.

Stability
A real-time stability study was conducted with the device stored in the storage conditions recommended in the package insert. Three lots of disks were tested throughout the 36-month claimed shelf life, and microbiological and chemical performance results were within the expected range which is acceptable. Stability and storage information is provided in the package insert.

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The qualitative Liofilchem Ceftobiprole BPR 5 µg Disc results were compared to the qualitative categorical interpretation (S/I/R) based on the minimum inhibitory concentration (MIC) values obtained from reference broth microdilution (BMD) to assess the categorical agreement (CA) and error rates. The study was conducted at one internal testing site. Three

independent operators participated in reading test results with isolates evenly distributed to mimic multiple testing sites. Testing was performed utilizing Mueller Hinton agar media. The reference BMD method was performed per CLSI M07 guidelines.

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 16-18 hours. At the end of the appropriate incubation, the Ceftobiprole BPR 5 µg Disc categorical interpretations as determined by zone edges at the point of complete inhibition (inhibition zone) were compared to categorical interpretations as determined by MIC results obtained with the CLSI reference broth microdilution method.

Clinical:
Clinical testing was performed using a total of 557 clinical isolates including 282 Enterobacterales (186 isolates of *Klebsiella pneumoniae*, 63 isolates of *Escherichia coli*, and 33 isolates of *Enterobacter cloacae*), and 275 *Staphylococcus aureus.* The clinical testing included 216 (38.8%) contemporary isolates (isolated no longer than 6 months prior to testing) and 341 (61.2%) stock isolates (isolated more than 6 months prior to testing).

Challenge:
Challenge testing was performed at one site using a total of 85 challenge isolates including 35 Enterobacterales (18 isolates of *Klebsiella pneumoniae*, 11 isolates of *Escherichia coli*, 6 isolates of *Enterobacter cloacae*), and 50 *Staphylococcus aureus.*

Performance results for the total 642 clinical and challenge isolates are shown in **Table 4**.

Table 4: Performance of the Ceftobiprole BPR 5 µg Disc vs. BMD

	Total	CA#	CA%	#S	#I	#R	MIN	MAJ	VMJ
Enterobacterales [Breakpoints (mm): ≥23 (S), 21-22 (I), ≤20(R)]									
Clinical	282	278	98.6	83	2	197	3	1	0
Challenge	35	35	100	3	0	32	0	0	0
Combined	317	313	98.7	86	2	229	3	1	0
***Staphylococcus aureus* [Breakpoints (mm), ≥16 (S), 14-15 (I), ≤13 (R)]**									
Clinical	275	262	95.3	263	12	0	7	0	0
Challenge	50	46	92.0	14	36	0	4	0	0
Combined	325	308	94.8	277	48	0	11	0	0

CA – Category Agreement
S – Susceptible isolates
I – Intermediate isolates
R – Resistant isolates
MIN – minor errors
MAJ – major errors
VMJ – very major errors

Category Agreement (CA) is when the device result interpretation agrees exactly with the comparator result interpretation.

The performance of the Ceftobiprole BPR 5 µg Disc as compared to the reference method MIC for Enterobacterales (**Table 4**) is acceptable with 98.7% CA. There were three minor errors and no very major errors. There was one major error (1.1%, 1/88 susceptible isolates), which is acceptable.

The performance of the Ceftobiprole BPR 5 µg Disc as compared to the reference method for *S. aureus* (**Table 4**) is acceptable with 94.8% CA. There were 11 minor errors and no major or very major errors.

Testing/Reporting Non-Indicated Species: 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 in the device labeling to address testing 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.

Resistance Isolates:

A total of 317 clinical and challenge Enterobacterales isolates and 325 clinical and challenge *S. aureus* isolates were tested when the Ceftobiprole BPR 5 µg Disc was compared to the interpretive category based on MIC values determined by the reference method. However, an insufficient number of resistant isolates were available for testing for *S. aureus*. To address the lack of resistant strains encountered during the clinical evaluation, the following limitation was applied to ceftobiprole testing in the device labeling:

The ability of the Antibiotic Disc to detect resistance or non-susceptibility to antimicrobials as shown below is unknown because resistant strains were not available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.
Ceftobiprole: Staphylococcus aureus.

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 Ceftobiprole

Organism	Disk Diffusion (Zone diameters in mm)[a]		
	Susceptible	Intermediate	Resistant
Staphylococcus aureus	≥16	14-15	≤13
Enterobacterales[b]	≥23	21-22	≤20

[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.

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/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria). The protocol outlined the specific procedures and acceptance criteria that Liofilchem Inc. intends to use to evaluate the Ceftobiprole BPR 5 µg Disc when revised breakpoints for ceftobiprole are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Liofilchem Inc. will update the Ceftobiprole BPR 5 µg Disc 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.