510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K180886

B. Purpose for Submission:

To obtain a substantial equivalence for the addition of Delafloxacin at concentrations of 0.002-32 µg/mL for susceptibility testing of non-fastidious Gram negative organisms

C. Measurand:

Delafloxacin 0.002-32 µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test growth based detection

E. Applicant:

Liofilchem s.r.l.

F. Proprietary and Established Names:

Liofilchem MIC Test Strip (MTS), Delafloxacin 0.002-32 µg/mL

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   II

3. Product code:

   JWY - Manual Antimicrobial Susceptibility Test Systems

4. Panel:

   83 – Microbiology

H. Intended Use:

1. Intended use(s):

   The Liofilchem® MIC Test Strip (MTS) 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.

   The Delafloxacin MTS at concentrations of 0.002-32 µg/mL should be interpreted at 16-20 hours of incubation.

   Delafloxacin has been shown to be active both clinically and *in vitro* against the non-fastidious bacteria listed below according to the FDA drug label:

   Gram-negative bacteria
   Escherichia coli
   Klebsiella pneumoniae
   Enterobacter cloacae
   Pseudomonas aeruginosa

   Delafloxacin has been shown to be active *in vitro* only against the non-fastidious bacteria listed below according to the FDA drug label:

   Klebsiella (Enterobacter) aerogenes
   Klebsiella oxytoca
   Proteus mirabilis

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   - For prescription use

   - The ability of the Liofilchem MIC Test Strip (MTS) to detect resistant isolates with the following drug/bacterial species combinations is unknown because resistant isolates were either not available or an insufficient number was encountered at the time of comparative testing.

     Delafloxacin: *Klebsiella (Enterobacter) aerogenes*

- Characterization of Topoisomerase IV and DNA gyrase quinolone-resistance determining regions (QRDRs) and altered efflux resistance mechanisms was not available for organisms at the time of comparative testing, and therefore the performance of Liofilchem MIC Test Strip Delafloxacin MTS for non-fastidious Gram negative bacilli with these resistance mechanisms is unknown for the following: *Enterobacteriaceae*, *P. aeruginosa*

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Delafloxacin MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of Delafloxacin across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. One side of the strip is labelled with the Delafloxacin code (DLX) and the MIC reading scale in µg/mL. When the MIC Test Strip is applied onto an inoculated agar surface, the preformed exponential gradient of antimicrobial agent is immediately transferred to the agar matrix. After 16- 20 hours incubation, a symmetrical inhibition ellipse centered along the strip is formed. The MIC is read directly from the scale in terms of µg/mL at the point where the edge of the inhibition ellipse intersects the MIC Test Strip. Since MTS strip generates MIC values which fall between two-fold dilutions for interpretation, the MIC value read is recorded to the next two-fold dilution value.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Liofilchem MTS, vancomycin

2. Predicate 510(k) number(s):

   K153687

3. Comparison with predicate:

Table 1: Comparison with the Predicate Device

Similarities		
Item	Device Liofilchem MTS, Delafloxacin (K180886)	Predicate Liofilchem MTS, vancomycin (K153687)
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Media	Mueller Hinton agar	Same
Inoculation	Isolated colonies from culture in suspension equivalent to 0.5 McFarland. Inoculum is applied manually using the manual plate inoculation method or plate rotator for even distribution of inoculum	Same
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip	Same
Result	MIC	Same

Differences		
Item	Device Liofilchem MTS, Delafloxacin (K171906)	Predicate Liofilchem MTS, vancomycin (K153687)
Antibiotic	Delafloxacin code (DLX)	Vancomycin code (VA)
Incubation	35 ± 2°C for 16 - 20hrs	35 ± 2°C for 24 hours

K. Standard/Guidance Document Referenced:

- Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.
- CLSI M07-A10 "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, Tenth Edition January 2015".
- CLSI M100-S26 "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement, January 2016".

L. Test Principle:

MTS are made of specialized paper impregnated with a predefined concentration gradient of antibiotic, across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. When the MIC Test Strip is applied onto an inoculated agar surface, the preformed exponential gradient of antimicrobial agent is immediately transferred to the agar matrix. After 16-20 hours incubation, a symmetrical inhibition ellipse centered along the strip is formed. The MIC is read directly from the scale in terms of µg/mL at the point where the edge of the inhibition ellipse intersects the strip MIC Test Strip.

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 0.125µg/mL is considered to be the same as 0.12µg/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.

M. Performance Characteristics:

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility testing was conducted at three sites using ten gram negative organisms. Each isolate was tested in triplicate over three days. The reproducibility panel included two *E. coli,* two *K. pneumoniae*, two *E. cloacae*, one *P. mirabilis*, and three *P. aeruginosa* isolates. The mode of MIC value was pre-determined 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.

b. Linearity/assay reportable range:

Not applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Quality Control (QC) Testing:

The QC isolates recommended by both FDA and 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 MTS and reference methods. The results are summarized in Table 2 below. The quality control results are acceptable.

Table 2: Delafloxacin MTS QC Results

Organism	Concentration (µg/mL)	Reference	MTS
E. coli ATCC 25922 Expected Result: 0.008-0.03 µg/mL	0.004		
	0.008		4
	0.015	47	42
	0.03	14	15
	0.06		
P. aeruginosa ATCC 27853 Expected Result: 0.12-0.5 µg/mL	0.06		
	0.12	2	11
	0.25	53	50
	0.5	6	
	1		

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. Inoculum density checks were performed and the colony counts obtained for each QC strain were within the recommended range of approximately 1x 10^8 CFU/mL. Colony counts was 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.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Results obtained with Liofilchem MIC Test Strip (MTS) with Delafloxacin were compared to results obtained from frozen reference MIC panels. Reference panels were prepared and interpreted as outlined in the recommendations in CLSI document M7-A10.

Isolated colonies from an overnight blood 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 plates in and

inverted position at 35°C ±2 for 16-20 hours. At the end of incubation, the MIC value where the edge of the inhibition ellipse intersects the strip was compared to the reference method.

Growth Rate:
The growth rate for the Liofilchem MIC Test Strip (MTS) with Delafloxacin was 100%

Clinical:
Clinical testing was performed at three US sites. A total of 360 clinical isolates were tested which included 240 *Enterobacteriaceae* isolates (15 *K. aerogenes*, 45 *E. cloacae*, 90 *E. coli*, 15 *K. oxytoca*, 60 *K. pneumoniae*, 15 *P. mirabilis*) and 120 *P. aeruginosa.* 65.6% of the clinical isolates were collected within 6 months of isolation.

Challenge:
Challenge testing was performed at one internal site. A total of 88 challenge isolates were tested which included 68 *Enterobacteriaceae* isolates (5 *K. aerogenes*, 14 *E. cloacae*, 21 *E. coli*, 5 *K. oxytoca*, 20 *K. pneumoniae*, 3 *P. mirabilis*) and 20 *P. aeruginosa* isolates.

The total of 448 clinical and challenge isolates is summarized in Table 3 below.

Table 3: Overall Performance of Clinical and Challenge Isolates (Combined)

Delafloxacin	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA %	#R	min	maj	vmj
Enterobacteriaceae (all) Clinical	240	237	98.8	230	227	98.7	236	98.3	60	4	0	0
Challenge	68	66	97.1	53	51	96.2	66	97.1	59	2	0	0
Combined	308	303	98.4	283	278	98.2	302	98.1	119	6	0	0
P. aeruginosa Clinical	120	119	99.2	113	112	99.1	112	93.3	31	8	0	0
Challenge	20	18	90.0	7	5	71.4	20	100	17	0	0	0
Combined	140	137	97.9	120	117	97.5	132	94.3	48	8	0	0
All Organisms	448	440	98.2	403	395	98.0	434	96.9	167	14	0	0

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

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

The overall performance of all *Enterobacteriaceae* isolates is acceptable with 98.4% EA and 98.1% CA. There were six minor discrepancies and no major or very major errors.

The overall performance of *P. aeruginosa* is acceptable with 97.9% EA and 94.3% CA. There were eight minor errors and no major or very major errors.

The overall performance of all organisms combined is acceptable with 98.2% EA and 96.9% CA.

Resistance Mechanism:

Molecular characterization was not evaluated for all organisms as this information was not available of the time of testing. This was addressed by adding the following footnote in the labeling:

> *"Characterization of Topoisomerase IV and DNA gyrase quinolone-resistance determining regions (QRDRs) and altered efflux resistance mechanisms was not available for organisms at the time of comparative testing, and therefore the performance of Liofilchem MIC Test Strip Delafloxacin MTS for non-fastidious Gram negative bacilli with these resistance mechanisms is unknown for the following: Enterobacteriaceae, P. aeruginosa"*

b. Matrix comparison:

Not Applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not Applicable

b. Clinical specificity:

Not Applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Delafloxacin are as listed in Table 5.

Table 5: FDA Interpretive Criteria for Delafloxacin (µg/mL)

Organisms	S	I	R
Enterobacteriaceae	≤0.25	0.5	≥1
P. aeruginosa	≤0.5	1	≥2

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.