510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K162854

B. Purpose for Submission:

To obtain a substantial equivalence determination for the Liofilchem MIC Test Strip (MTS) containing Meropenem at concentrations of 0.002-32µg/mL for susceptibility testing of*, E. coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Pseudomonas aeruginosa*

C. Measurand:

Meropenem 0.002-32 µg/mL

D. Type of Test:

Quantitative AST growth based detection

E. Applicant:

Liofilchem s.r.l.

F. Proprietary and Established Names:

Liofilchem MIC Test Strip (MTS)-Meropenem 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 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 non-fastidious Gram negative and Gram positive aerobic bacteria (for example, *Enterobacteriaceae*, *Pseudomonas*, *Enterococcus* and *Staphylococcus* species) and fastidious bacteria (for example, anaerobes, *Haemophilus* and *Streptococcus* species and *N. gonorrhoeae*). 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.

2. Indication(s) for use:

The Liofilchem MIC Test Strip (MTS) is a quantitative method intended for the *in vitro* determination of antimicrobial susceptibility of non-fastidious Gram negative and Gram positive aerobic bacteria (for example, *Enterobacteriaceae*, *Pseudomonas*, *Enterococcus* and *Staphylococcus* species) and fastidious bacteria (for example, anaerobes, *Haemophilus* and *Streptococcus* species and *N. gonorrhoeae*). 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 indications for use of this 510(k) is specifically for the Meropenem MTS at concentrations of 0.002-32 µg/mL.

The non-fastidious bacteria that have been shown to be active both clinically and in vitro against Meropenem according to the FDA label are:

Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

3. Special conditions for use statement(s):

   For prescription use

   The following limitation is included in the Liofilchem Meropenem MIC Test Strip (MTS) package insert supplement:

   The ability of the Liofilchem MIC Test Strip (MTS) to detect resistance is unknown for the following antibiotic/organism combination, because an insufficient number of resistant isolates were available during the comparative testing:
   Meropenem-Proteus mirabilis

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The meropenem MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of meropenem across 15 two-fold dilutions like those of a conventional MIC method. One side of the strip is labelled with the meropenem code (MRP) 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.

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	Predicate K153687
Intended Use	Quantitative susceptibility to antimicrobial agents against specified gram negative organisms	Same
Media	Mueller Hinton agar	Same
Inoculation	Isolated colonies from culture in suspension equivalent to 0.5 McFarland. Inoculum is applied applied to agar with swab manually	Same
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip	Same
Result	MIC	Same

Differences		
Item	Device	Predicate
Antibiotic	Meropenem	Vancomycin
Incubation	35 ± 2°C for 16- 20hrs	35 ± 2°C for 24hrs

K. Standard/Guidance Document Referenced:

"Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA"

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 like those of a conventional MIC method. 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 (if/when applicable):

a. Precision/Reproducibility:

Reproducibility testing was performed using five *Pseudomonas aeruginosa* isolates and five *Enterobacteriaceae* isolates (three *E. coli,* one *K. pneumoniae,* and one *Enterobacter cloacae*). These ten organisms were tested at three sites in triplicates on three days. The mode of MIC value was determined and the reproducibility was calculated based on the number of MIC values that fell within +/- one doubling dilution of the mode. 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):

The recommended Quality Control (QC) isolates were tested a sufficient number of times at all three sites with acceptable results in comparison to the reference method. All results were within the expected range greater than 95% of the time. The results are summarized in Table 2.

Table 2: Meropenem MTS QC results

Organism	Concentration (µg/mL)	Reference	MTS
E. coli ATCC 25922 Expected Results 0.008-0.06 µg/mL	≤0.002		
	0.004		
	0.008		
	0.015	12	15
	0.03	45	45
	0.06	3	
	0.12		
P. aeruginosa ATCC 27853 Expected Results 0.25 – 1 µg/mL	0.015		
	0.03		
	0.06		
	0.12		
	0.25	33	31
	0.5	19	27
	1	8	2
	2		

The QC results were acceptable.

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:

Clinical testing was conducted at three sites (two U.S. sites and one outside the U.S.). A total of 327 organisms were tested and all organisms grew in the studies. All isolates tested were fresh. The clinical testing included 278 (85%) fresh (isolated no longer than seven days prior to testing) and 49 (15%) recent clinical isolates (isolated no longer than one year prior to testing). The study included 192 *Enterobacteriaceae* and 135 *Pseudomonas aeruginosa* clinical isolates. The *Enterobacteriaceae* tested were *Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis.*

A total of 75 challenge isolates were also evaluated (31 *Enterobacteriaceae* and 44 *P. aeruginosa*. The performance is shown in Table 3.

Table 3: Performance of *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates

Meropenem	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	min	maj	vmj
Enterobacteriaceae												
E. coli												
Clinical	103	102	99	99	98	99	102	99	13	1	0	0
Challenge	15	15	100	15	15	100	14	93.3	2	1	0	0
Combined	118	117	99.2	114	113	99.1	116	98.3	15	2	0	0
K. pneumoniae												
Clinical	58	58	100	54	54	100	58	100	9	0	0	0
Challenge	14	13	92.9	13	12	92.3	11	78.6	9	3	0	0
Combined	72	71	98.6	67	66	98.5	69	95.8	18	3	0	0
P. mirabilis												
Clinical	31	30	96.8	31	30	96.8	31	100	0	0	0	0
Challenge	2	2	100	2	2	100	2	100	1	0	0	0
Combined	33	32	97.0	33	32	97	33	100	1	0	0	0
Enterobacteriaceae	223	220	98.7	214	211	98.6	218	97.8	34	5	0	0

Meropenem	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	min	maj	vmj
Pseudomonas aeruginosa												
Clinical	135	123	91.1	105	93	88.6	129	95.6	43	6	0	0
Challenge	44	42	95.5	17	15	88.2	44	100	40	0	0	0
All *P. aeruginosa*	179	165	92.2	122	108	88.5	173	96.6	83	6	0	0
All organisms	402	385	95.8	336	319	94.9	391	97.3	117	11	0	0

EA - Essential Agreement **maj** – major discrepancies
CA - Category Agreement **vmj**- very major discrepancies
R- resistant isolates **min**- minor discrepancies

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.

In the challenge study, low CA was observed for *K. pneumoniae* (78.6%, 11/14); however, this was mainly due to three minor errors. The % Evaluable EA was 92.3%.

Enterobacteriaceae: The overall performance for *Enterobacteriaceae* was acceptable, with an EA of 98.7%, a CA of 97.8%, and a minor discrepancy rate of 2.24% (5/223).

Pseudomonas aeruginosa: The overall performance for *P. aeruginosa* was acceptable, with an EA of 92.2%, a CA of 96.6%, and a minor discrepancy rate of 3.35% (6/179).

Resistant Organisms:
A total of 117 resistant isolates were identified out of 402 organisms tested (29.1%) in the combined challenge and clinical study for the Liofilchem MIC Test Strip (MST). However, *P. mirabilis* had an insufficient number of resistant isolates tested during the comparative study. This was addressed by adding the following limitation in the Liofilchem Meropenem MIC Test Strip (MTS) package insert supplement:

The ability of the Liofilchem MIC Test Strip (MTS) to detect resistance is unknown for the following antibiotic/organism combination, because an insufficient number of resistant isolates were available during the comparative testing:
Meropenem-Proteus mirabilis

MIC Trends:
Using the combined clinical and challenge data for *Pseudomonas aeruginosa* an analysis of the trending was conducted using 122 evaluable results plus an additional 13 results where an assignment for trend analysis was made through other considerations. The combined data of 135 results constitute the number of evaluable data for trend analysis. The analysis is presented in Table 4.

Table 4: Trending Summary of Clinical and Challenge Isolates Results of *P. aeruginosa

	Total No Isolates	≤-1	Exact	≥+1
Clinical	105	20	48	37
Challenge	30	0	6	24
Combined	135	20 (14.8%)	54 (40%)	61 (45.2%)

* Analysis conducted using the number of evaluable results for trending analysis. Difference is 30.4% (95% CI: 19.7% to 40.2%)

A higher MIC reading trend was observed in the overall performance of *Pseudomonas aeruginosa* compared to the CLSI broth micro-dilution, which raises concerns for potential major errors. This trending and the potential for occurrence of major error(s) for Meropenem when testing clinical and challenge isolate results with Liofilchem MIC Test Strip (MTS), was addressed in the labeling by adding the following footnote under the performance characteristics Table:

The Liofilchem MIC Test Strip (MTS) Meropenem MIC values tended to be one or more doubling dilution higher when testing P. aeruginosa compared to the CLSI reference broth microdilution (for 135 P. aeruginosa isolates tested with evaluable MIC results for trending, 14.8% were one, two or more doubling dilutions lower, 40% were exact, and 61% were one, two or more dilution higher compared to the CLSI broth microdilution results).

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:

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

Organisms	S	I	R
Enterobacteriaceae	≤1	2	≥4
Pseudomonas aeruginosa	≤2	4	≥8

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.