510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K173307

B. Purpose for Submission:

To obtain a substantial equivalence determination of the Liofilchem MIC Test Strip (MTS) containing Meropenem/vaborbactam at concentrations of 0.016/8 – 256/8 µg/mL for susceptibility testing of select gram negative bacilli

C. Measurand:

Meropenem/vaborbactam 0.016/8 – 256/8 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), Meropenem/vaborbactam 0.016/8 – 256/8 µg/mL

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code(s):

   LWY – Manual Antimicrobial Test Systems

4. Panel:

   Microbiology (83)

H. Intended Use/Indications for 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 Meropenem/vaborbactam MTS at concentrations of 0.016/8-256/8 µg/mL should be interpreted at 16-20 hours of incubation.

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

   Enterobacter cloacae species complex
   Escherichia coli
   Klebsiella pneumoniae

   Meropenem/vaborbactam has been shown to be active *in vitro* against susceptible isolates of the following microorganisms:

   Citrobacter freundii
   Citrobacter koseri
   Enterobacter aerogenes
   Klebsiella oxytoca
   Proteus mirabilis
   Providencia spp.
   Serratia marcescens

2. Indications for Use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For Prescription Use Only

   Limitation:

   > "*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:
Meropenem/vaborbactam: Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Klebsiella oxytoca, Proteus mirabilis, Providencia spp., Serratia marcescens"

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Meropenem/vaborbactam MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of meropenem/vaborbactam across 15 two-fold dilutions like those dilutions of a conventional MIC method. One side of the strip is labelled with the Meropenem/vaborbactam code (M/V) and the MIC reading scale is 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. The MIC Test Strip is single use only. 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:

Similarities		
Item	**Device: Liofilchem MTS, Meropenem/vaborbactam (K173307)**	**Predicate Device: Liofilchem MTS, Vancomycin (K153687)**
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Media	Mueller Hinton agar	Same
Inoculum	Isolated colonies from culture in suspension equivalent to 0.5 McFarland. Inoculum is applied to agar with swab manually or with rotation plate	Same

Similarities		
Item	**Device: Liofilchem MTS, Meropenem/vaborbactam (K173307)**	**Predicate Device: Liofilchem MTS, Vancomycin (K153687)**
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip	Same
Result	MIC (µg/mL)	Same
Differences		
Item	**Device: Liofilchem MTS, Meropenem/vaborbactam (K173307)**	**Predicate Device: Liofilchem MTS, vancomycin (K153687)**
Antimicrobial Agent	Meropenem/vaborbactam	Vancomycin
Incubation	35°C ± 2°C for 16-20 hours	35°C ± 2°C for 24 hours

K. Standard/Guidance Document Referenced (if applicable)

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

- CLSI M07-10, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Tenth Edition" (January 2015)

- CLSI M100-S27, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-Seventh Informational Supplement (January 2017)

L. Test Principle:

MIC Test Strips (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 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 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 0.125µg/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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study testing the Liofilchem MIC Test Strip (MTS) containing Meropenem/vaborbactam was conducted at three clinical sites using ten isolates of Gram-negative bacilli consistent with the Intended Use. Testing was performed on three separate days and in triplicate for a total of 270 data points among the sites. The isolates tested in the reproducibility study included *Escherichia coli* (four isolates), *Klebsiella pneumoniae* (three isolates), *Enterobacter cloacae* (two isolates), and *Pseudomonas aeruginosa* (one isolate). The mode MIC value was determined and the reproducibility was calculated based on MIC values that fell within +/- one doubling dilution from the mode MIC value. Both intra-site and inter-site reproducibility for Meropenem/vaborbactam MTS was calculated. There were no off-scale MIC results.

The combined reproducibility results for all three sites were acceptable and demonstrated ≥95% reproducibility.

b. Linearity/assay reportable range:

Not applicable

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

Quality Control (QC) Testing

FDA/CLSI recommended QC organisms were tested throughout the comparative testing at three study sites. The organisms tested were *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC BAA-1705. These recommended QC organisms were tested a minimum of 20 times/site by both the Liofilchem MTS, Meropenem/vaborbactam and with the CLSI broth microdilution reference method.

Both the auto-dilution and the manual dilution methods were within the expected range >95% of the time. In instances where any organism was out of range for the reference method, all testing data from that day was invalid and repeated. The Meropenem/vaborbactam MIC QC results are summarized in Table 1. All QC results were acceptable.

Table 1. Quality Control Results Summary for Meropenem/vaborbactam MTS

Organism	Concentration (µg/mL)	Reference	MTS
Pseudomonas aeruginosa ATCC 27853 Expected Range 0.12/8 – 1/8 µg/mL	0.06/8		
	0.12/8		
	0.25/8	45	11
	0.5/8	13	48

	1/8	2	1
	2/8		
Klebsiella pneumoniae ATCC BAA-1705 Expected Range 0.015/8 – 0.06/8 µg/mL	0.008/8		
	0.015/8		
	0.03/8	52	3
	0.06/8	9	58
	0.12/8		

Inoculum Density Check

The inoculum was prepared to achieve a 0.5 McFarland standard turbidity. Colony counts were performed periodically at each site as part of QC and reproducibility procedures as well as during clinical studies to demonstrate that the inoculum procedure results were in the expected CFU/mL (approximately $1x10^8$ CFU/mL).

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 the Liofilchem MIC Test Strip (MTS), Meropenem/vaborbactam were compared to results obtained with the CLSI broth microdilution reference panel. The reference panel contained two-fold serial dilutions with a range of ≤ 0.016 to ≥ 256 µg/mL. The testing conditions for the reference method were consistent with CLSI guideline, M07-A10.

The Liofilchem MIC Test Strip (MTS), Meropenem/vaborbactam was evaluated by three sites located in the United States. Every clinical isolate was tested one time by Meropenem/vaborbactam MTS and the reference method using the same initial standardized suspension.

Of the 390 clinical *Enterobacteriaceae*, there were 185 (47.4%) fresh isolates that were tested within seven days of isolation, 138 (35.4%) recent isolates that were tested within one year of isolation, and 67 (17.2%) stock isolates that were tested within three years of isolation. All clinical strains grew in both the MTS agar plates

and the broth microdilution panels.

A total of 88 *Enterobacteriaceae* challenge isolates were also evaluated at one site.

The comparative study (both clinical and challenge organisms) included 478 *Enterobacteriaceae* isolates. The organisms included *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae, Proteus mirabilis*, *Providencia rettgeri*, and *Serratia marcescens*.

The performance of 478 clinical and challenge isolates is summarized in Table 2.

Table 2. Performance[‡] of *Enterobacteriaceae* Isolates

Organism Group	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#R	Min	Maj	Vmj
Enterobacteriaceae* ≤4/8 (Susceptible), 8/8 (Intermediate), ≥16/8 (Resistant)												
Clinical	390	379	97.2	349	346	99.1	389	99.7	1	1	0	0
Challenge	88	78	88.6	81	73	90.1	75	85.2	41	12	1	0
Combined	**478**	**457**	**95.6**	**430**	**419**	**97.4**	**464**	**97.1**	**42**	**13**	**1**	**0**

[‡]**EA** – Essential Agreement (+/- 1doubling dilution)
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
Min – Minor discrepancies
Maj – Major discrepancies
Vmj – Very major discrepancies

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. Evaluable results were defined as when both the reference method results and the Liofilchem MTS results were on-scale. Evaluable results were also defined as when the reference method results were on-scale and off-scale Liofilchem MTS results clearly did not agree within the accepted +/- one doubling dilution.

*Parenthesis show the Meropenem/vaborbactam MIC values that correspond to the interpretive categories of S/I/R.

Overall Performance:

The overall performance of the Meropenem/vaborbactam MIC Test Strip for *Enterobacteriaceae* is acceptable with an EA of 95.6% and CA of 97.1%. There were no very major errors, one major error (0.2% error rate, 1/425 susceptible organisms), and 13 minor errors (2.7% error rate, 13/478 total organisms).

Resistant Organisms:

A total of 42 resistant isolates were identified in the combined clinical (n=1) and challenge (n=41) study of the Meropenem/vaborbactam MTS out of 478 organisms (8.8%). However, the following organisms had either no resistant isolates or an insufficient number of resistant isolates were encountered during comparative testing: *Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Klebsiella oxytoca, Proteus mirabilis, Providencia rettgeri,* and *Serratia marcescens*. This was addressed by adding the following limitation in the package insert:

"*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:

Meropenem/vaborbactam: Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Klebsiella oxytoca, Proteus mirabilis, Providencia spp., Serratia marcescens"

Enzyme Group Characterization:

The FDA approved pharmaceutical antimicrobial agent package insert provides a detailed description of enzyme groups for organisms tested in the drug study. Enzyme characterization was conducted for *Enterobacteriaceae* to cover the majority of β-lactamase enzyme groups noted in the FDA drug label. The performance of the Liofilchem MTS Meropenem/vaborbactam study included evaluation of performance with isolates belonging to the enzyme groups as shown below.

***Enterobacteriaceae* (ESBLs)**

Enzyme characterization was conducted for claimed *Enterobacteriaceae* isolates for the following ESBLs: TEM, SHV, CTX-M. Meropenem/vaborbactam demonstrated acceptable performance against *Enterobacteriaceae* carrying these β-lactamase encoding genes.

***Enterobacteriaceae* (KPC and SME; serine carbapenemases)**

Enzyme characterization was conducted for claimed *Enterobacteriaceae* isolates for the following serine carbapenemases: KPC (*K. pneumoniae* carbapenemase [KPC]) and SME (*Serratia marcescens* enzyme). One major error was observed for *K. pneumoniae* with a MAJ rate of 3.2% (1/31). This *K. pneumoniae* isolate produced KPC-2, TEM-181, and SHV-11 of which Meropenem/vaborbactam should exhibit susceptibility; this resistance profile suggests other mechanisms of resistance. Further, *Enterobacteriaceae* isolates with genes encoding SME enzymes were not available at the time of testing and were not evaluated. This was addressed by adding the following footnote under the Performance Characteristics table:

"*Enzyme group characterization was not available for the following organisms at the time of comparative testing, and therefore the performance of Meropenem/vaborbactam is unknown: Enterobacteriaceae (SME)*"

***Enterobacteriaceae* (AmpC β-lactamases)**

Enzyme characterization was conducted for claimed *Enterobacteriaceae* isolates for the following AmpC β-lactamases: CMY, ACT. Meropenem/vaborbactam demonstrated acceptable performance against *Enterobacteriaceae* carrying these β-lactamase encoding genes.

***Enterobacteriaceae* (Other β-lactamases)**

Testing was conducted against *Enterobacteriaceae* isolates that are known to produce metallo-beta lactamases or oxacillinases with carbapenemase activity. However, Meropenem/vaborbactam is not active against these classes of beta-lactamases and

therefore, the following footnote was added in the labeling (Performance Characteristics table):

"*Meropenem/vaborbactam is not active against bacteria that produce metallo-beta lactamases or oxacillinases with carbapenemase activity*"

MIC Trends:

Using the combined clinical and challenge data for *Enterobacteriaceae*, an analysis of trending was conducted. This trending calculation considers MIC values that are determined to be one or more doubling dilution lower or higher compared to the reference method irrespective whether the device MIC values are on-scale or not. The evaluable data for trend analysis is presented in Table 3 for *Enterobacteriaceae*.

Table 3. Trending Analysis of Evaluable Clinical and Challenge Results for *Enterobacteriaceae*

Meropenem/ vaborbactam 0.016/8 – 256/8 µg/mL	Total Isolates[a]	Difference in MIC as Compared to the CLSI Reference Method				
		≥ 2 dilution lower	1 dilution lower	Exact	1 dilution higher	≥ 2 dilution higher
C. freundii	15	0	0	4 (26.67%)	11	0
		0 (0.00%)[b] 95% CI (0.00% to 20.39%)			11 (73.33%)[b] 95% CI (48.05% to 89.10%)	
C. koseri	12	0	0	5 (41.67%)	7	0
		0 (0.00%)[c] 95% CI (0.00% to 24.25%)			7 (58.33%)[c] 95% CI (31.95% to 80.67%)	
E. aerogenes	15	0	0	4 (26.67%)	11	0
		0 (0.00%)[d] 95% CI (0.00% to 20.39%)			11 (73.33%)[d] 95% CI (48.05% to 89.10%)	
E. cloacae	105	0	10	33 (31.43%)	61	1
		10 (9.52%)[e] 95% CI (5.26% to 16.65%)			62 (59.05%)[e] 95% CI (49.48% to 67.97%)	
E. coli	150	0	2	70 (46.67%)	67	11
		2 (1.33%)[f] 95% CI (0.37% to 4.73%)			78 (52.00%)[f] 95% CI (44.06% to 59.85%)	
K. oxytoca	12	0	0	1 (8.33%)	11	0
		0 (0.00%)[g] 95% CI (0.00% to 24.25%)			11 (91.67%)[g] 95% CI (64.61% to 98.51%)	
K. pneumoniae	121	0	8	45 (37.19%)	62	6
		8 (6.61%)[h] 95% CI (3.39% to 12.51%)			68 (56.20%)[h] 95% CI (47.30% to 64.71%)	

[a] Total number of evaluable results for trending analysis
[b] Difference: 73.33%: 95% CI (40.85% to 89.10%)
[c] Difference: 58.33%: 95% CI (22.50% to 80.67%)
[d] Difference: 73.33%: 95% CI (40.85% to 89.10%)
[e] Difference: 49.52%: 95% CI (37.60% to 59.42%)
[f] Difference: 50.67%: 95% CI (42.03% to 58.57%)
[g] Difference: 91.67%: 95% CI (55.33% to 98.51%)
[h] Difference: 49.59%: 95% CI (38.92% to 58.69%)
Note: A positive percent difference value indicates higher MIC when compared to the reference method

A higher MIC reading trend was observed in the overall performance of *C. freundii*, *C. koseri*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, and *K. pneumoniae* to CLSI broth microdilution, which raises concerns for potential major errors.

To address the high trending and the potential occurrence of major error(s) when using the Meropenem/vaborbactam MTS, the following statement was added as a footnote in the Performance Characteristics section of the labeling, "Drug Specific Supplement for MIC Test Strip (MTS), Meropenem-vaborbactam (M/V)":

> "*The Liofilchem MIC Test Strip (MTS) Meropenem/vaborbactam values tended to be in exact agreement or at least one doubling dilution higher when testing C. freundii, C. koseri, E. aerogenes, E. cloacae, E. coli, K. oxytoca, and K. pneumoniae compared to the CLSI reference broth microdilution.*"

The analysis of all other *Enterobacteriaceae* MIC data (i.e., *P. mirabilis*, *P. rettgeri*, *S. marcescens*) demonstrated no notable trending.

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 4. Interpretive Criteria for Meropenem/vaborbactam (FDA Drug Label)

Organism	FDA Interpretive Criteria for Meropenem/vaborbactam (µg/mL)		
	S	I	R
Enterobacteriaceae	≤4/8	8/8	≥16/8

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.