510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K170772

B. Purpose for Submission:

To obtain a substantial equivalence determination for the Liofilchem MIC Test Strip (MTS) containing clindamycin at concentrations of 0.016 -256 µg/mL for susceptibility testing of *Staphylococcus aureus*

C. Measurand:

Clindamycin 0.016-256 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), Clindamycin 0.016-256 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 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 Clindamycin MTS at concentrations of 0.016-256 µg/mL should be interpreted at 16-20 hours of incubation.

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

   Staphylococcus aureus (methicillin-susceptible strains)

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The clindamycin MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of clindamycin across 15 two-fold dilutions like those of a conventional MIC method. One side of the strip is labelled with the clindamycin code (CD) 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	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	Predicate
Antibiotic	Clindamycin (CD)	Vancomycin (VA)
Incubation	35 ± 2°C for 16 - 20hrs	35 ± 2°C for 24 hours

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):

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility testing was performed using ten *Staphylococcus aureus* isolates. These ten isolates 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 ±1 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 QC isolate was tested a sufficient number of times (i.e., at least 20/site) 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 below.

Table 2: Clindamycin MTS QC results

Organism	Concentration (µg/mL)	Reference	MTS
S. aureus ATCC 2213 Expected Result 0.06 – 0.25µg/mL	0.03		
	0.06	16	4
	0.12	42	50
	0.25	3	7

The inoculum was prepared to achieve a 0.5 McFarland standard turbidity. Colony counts were performed periodically at each site. Inoculum density checks were performed and the average colony counts of each QC strain were within the recommended range of approximately 1x 10^8 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:

Clinical testing was conducted at three sites (two U.S. and one non- U.S. sites). A total of 350 organisms were tested and all organisms grew in the studies. There were 251 (71.7%) isolates that were tested within seven days of collection and 99 (28.3%) isolates that were tested within one year of collection. The 350 organisms were 200 MSSA and 150 MRSA clinical isolates. There were also 75 challenge *Staphylococcus aureus* (11 MSSA and 64 MRSA) which result a total of 425 clinical and challenge isolates.

Results obtained with Liofilchem MIC Test Strip (MTS) with Clindamycin were compared to results obtained from frozen reference MIC panels. Reference panels were prepared and interpreted as outlined in CLSI recommendations in 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. Clindamycin is bacteriostatic; MIC is read at 80% inhibition. The performance is listed in Table 3 below:

Table 3: Performance of *Staphylococcus aureus* isolates*

Clindamycin	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA %	CA N	CA %	#R	min	maj	vmj
	***Staphylococcus* spp. ≤0.5 (Susceptible), 1-2 (Intermediate), ≥4 (Resistant)**											
MSSA												
Clinical	200	196	98.0	191	187	97.9	200	100	9	0	0	0
Challenge	11	11	100	9	9	100	11	100	3	0	0	0
Combined	211	207	98.1	200	196	98.0	211	100	12	0	0	0
MRSA												
Clinical	150	146	97.3	117	113	96.6	149	99.3	35	1	0	0
Challenge	64	61	95.3	33	30	90.9	63	98.4	38	1	0	0
Combined	214	207	96.7	150	143	95.3	212	99.1	73	2	0	0
Total *S. aureus*	**425**	**414**	**97.4**	**350**	**339**	**96.9**	**423**	**99.5**	**85**	**2**	**0**	**0**

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

The indicated methicillin-susceptible *Staphylococcus aureus* (MSSA) included twelve clindamycin resistant isolates. Methicillin-resistant *Staphylococcus aureus* (MRSA) was included to enhance the clindamycin resistant isolates for evaluation with a total of 85 resistant isolates. The clindamycin breakpoints in the FDA drug label are for the genus *Staphylococcus* spp. and there are no separate breakpoints for MRSA/MSSA. Therefore, the *Staphylococcus* spp. breakpoint was used for evaluation of performance for both MSSA and MRSA. Similar performance was observed for MRSA and MSSA.

The overall performance of *Staphylococcus aureus* was acceptable with EA 97.4% EA and 99.5% CA. There were no major or very major discrepancies.

Trending

Staphylococcus aureus was also evaluated for trending. This trending calculation takes into account MIC values that are determined to be ≤1 and ≥1 doubling-dilutions compared to the reference method irrespective whether the device MIC values are on-scale or not. The analysis showed that within EA, trending was observed for *Staphylococcus aureus.* The trending analysis was shown in Table 4:

Table 4: Trending Analysis of Evaluable Clinical and Challenge Results

Clindamycin 0.016- 256 µg/mL	Total [a]	Difference in MIC as Compared to the CLSI Reference Method				
		≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
S. aureus MSSA+MRSA	352	3	21	167 (47.44%)	153	8
		24 (6.82%) [b] 95% CI (4.62% to 9.94%)			161 (45.74%) [b] 95% CI (40.61% to 50.96%)	

[a] Total number of evaluable results for trending analysis
[b] Difference: -38.92%; 95% CI (-44.59% to -32.91%)

A higher MIC reading trend was observed in the overall performance of *Staphylococcus aureus* (MSSA+MRSA) compared to the CLSI broth microdilution reference method, which raises concerns for potential major discrepancy. This trending and the potential for occurrence of major discrepancies were addressed by adding the following footnote in the Performance Characteristics section of the labeling, "Drug Specific Supplement for Clindamycin MIC Test Strip (MTS)":

"The Liofilchem MIC Test Strip (MTS) clindamycin values tended to be in exact agreement or at least one doubling dilution higher when testing S. aureus compared to the CLSI reference broth microdilution."

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 Clindamycin (µg/mL)

Organisms	S	I	R
Staphylococcus aureus	≤0.5	1-2	≥4

Because macrolide-inducible resistance to clindamycin occurs in some isolates of macrolide-resistant bacteria, macrolide-resistant *Staphylococcus aureus* isolates should be screened for induction of clindamycin resistance using Inducible Clindamycin Resistance Supplemental Test. The footnote below is included under the clindamycin interpretative criteria section:

> *"Inducible clindamycin resistance supplemental test is required for Staphylococcus aureus isolates that test erythromycin resistant and clindamycin susceptible or intermediate before reporting the isolate as clindamycin susceptible (CLSI M100 S26)."*

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.