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

A. 510(k) Number:

K170892

B. Purpose for Submission:

To obtain a substantial equivalence determination for the Liofilchem MIC Test Strip (MTS) containing Tedizolid in concentrations of 0.002 – 32 µg/mL for susceptibility testing of *Staphylococcus aureus* (including methicillin-resistant isolates) and *Enterococcus faecalis*.

C. Measurand:

Tedizolid 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), Tedizolid 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 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 Tedizolid MTS at concentrations of 0.002– 32 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 Tedizolid according to the FDA label are:

Staphylococcus aureus (including methicillin resistant and methicillin susceptible isolates)
Enterococcus faecalis

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   Prescription use only

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Tedizolid MIC Test Strip (MTS) is made of special high quality paper impregnated with a predefined concentration of gradient Tedizolid, across 15 two-fold dilutions similar to dilutions used in conventional MIC testing. The face up side of the strip is labelled with the Tedizolid code (TDZ) 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 diffuses into the agar for over an hour. After 16-20 hours incubation, a symmetrical inhibition ellipse centered along the strip is formed. The MIC is read directly form 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 MIC Test Strip (MTS) – Vancomycin 0.016 – 256 µg/mL

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	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 (µg/mL)	Same

Differences		
Item	Device	Predicate K153687
Antibiotic	Tedizolid	Vancomycin
Incubation	35 ± 2°C for 16-20 hours	35 ± 2°C for 24 hours

K. Standard/Guidance Documents Referenced (if applicable):

"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 four methicillin-sensitive *Staphylococcus aureus* isolates (MSSA), three methicillin-resistant *Staphylococcus aureus* isolate (MRSA), and three *Enterococcus faecalis* (vancomycin-sensitive) isolates. These ten organisms were tested at three sites in triplicate 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 isolates were 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: Quality Control Test Results for Tedizolid

Organism	Expected Result	Concentration (µg/mL)	Reference	MTS
S. aureus ATCC 29213	0.25 – 1 µg/mL	0.012		
		0.25	27	41
		0.5	33	30
		1		
		2	1*	1*
E. faecalis ATCC 29212	0.25 – 1 µg/mL	0.012		
		0.25	35	4
		0.5	26	60
		1		8
		2		

*One QC isolate was out of range for both reference and MTS method on the same day from Site 3. As stated in the protocol, subsequent testing was performed the next day which resulted in MIC values within range.

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 1 x 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 U.S sites. A total of 300 organisms were tested and all organisms grew in the study. Of these, 95 (31.7%) were tested within seven days of collection, 118 (39.3%) were tested within one year of collection and 87 (29.0%) were tested within three years of collection. The clinical study included 180 *S. aureus* (75 MSSA and 105 MRSA) and 120 *E. faecalis* isolates. In addition to clinical isolates, 46 *S. aureus*, 47 *Enterococcus* sp. (11 *E. faecalis* and 36 *E. faecium*), and 25 coagulase negative *Staphylococcus* sp. challenge isolates were tested for a

combined total of 418 isolates.

Results obtained with Liofilchem MIC Test Strip (MTS) with Tedizolid 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 eillipse intersects the strip was compared to the reference method. The performance is listed in Table 3 below:

Table 3: Performance of *S. aureus* (75 MSSA and 105 MRSA clinical isolates) and 120 *E. faecalis* clinical isolates

	EA Tot[1]	EA N	EA%	Eval. EA N	Eval. EA%	CA N	CA%	#NS	#R	min	maj	vmj
S. aureus ≤0.5 (Susceptible), 1 (Intermediate), ≥2 (Resistant)												
S. aureus (combined MSSA and MRSA-Clinical)	180	180	100	180	100	179	99.4	N/A	0	1	0	0
S. aureus (combined clinical and challenge isolates)	226	226	100	226	100	221	97.8	N/A	6	5	0	0
Staphylococcus sp. (combined challenge[2] and clinical isolates)	251	249	99.2	247	99.2	245	97.6	N/A	30	6	0	0
E. faecalis ≤0.5 (Susceptible), -- (Intermediate), -- (Resistant)												
E. faecalis (vancomycin susceptible)	120	120	100	120	100	113	94.2	0	N/A	N/A	7[3]	0
E. faecalis (combined clinical and challenge isolates)	131	128	97.7	131	97.7	124	94.7	4	N/A	N/A	7	0
Enterococcus sp. (combined challenge[4] and clinical isolates)	167	164	98.2	167	164	160	95.8	35	N/A	N/A	7	0
All isolates	418	413	98.8	414	98.8	405	96.9	35	30	6	7	0

[1]**EA** – Essential Agreement
CA – Category Agreement
NS – Non-susceptible isolates
#R – Resistant isolates
maj – major discrepancies
vmj – very major discrepancies
min – minor discrepancies

[2]The challenge isolates tested consisted of 46 *S. aureus* and 25 coagulase negative *Staphylococcus* sp. The coagulase negative isolates consisted of *S. epidermidis* (15), *S. hominis* (2), *S. haemolyticus* (5), *S. simulans* (1) and *S. capitis* (1). Breakpoints for coagulase negative strains have not been established; however, susceptibility status was determined using the breakpoint for *S. aureus.*

[3]The overall major error rate for *E. faecalis* (clinical and challenge) was 5.5%. All 7 major errors were one dilution apart which falls within essential agreement. Based on the essential agreement, the adjust major error rate is 0.

[4]The challenge isolates tested consisted of 11 *E. faecalis* and 36 *E. faecium* strains. Even though breakpoints have not been established for *E. faecium* susceptibility status was determined using the breakpoint for *E. faecalis.* Based on these criteria, 35 *E. faecium* isolates were determined to be "non-susceptible" and all were accurately detected.

Essential agreement (EA) is when the Liofilchem MIC Test Strip (MTS) results agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the Liofilchem MIC Test Strip (MTS) result interpretation agrees exactly with the reference panel result interpretation.

For clinical and challenge isolates tested with the Liofilchem MTS for Tedizolid, the %EA and %CA each met the acceptance criteria of greater than or equal to 90% (Table 3). There were no major errors when testing *S. aureus*, seven major errors with *E. faecalis* and no very major errors for either organism which met the acceptance criteria. All seven major errors (5.5% major error rate) with *E. faecalis* were within essential agreement (i.e., BMD = 0.5, MTS = 1) and this was considered acceptable. Taking the seven values within essential agreement into consideration, the major discrepancy rate became 0.

MIC Trends:

Using the data provided by the sponsor in the diagonal table format recommended in the AST Guidance, an analysis was conducted to check for trending in MIC values. This trending calculation takes into account MIC values that are determined to be ≤1 and ≥1 doubling dilutions compared to the reference method irrespective of whether the device MIC values are on-scale or not. A higher MIC reading trend was observed in the overall performance for both *S. aureus* and *E. faecalis* isolates compared to the CLSI broth micro-dilution reference method, as summarized in Table 4.

Table 4: Trending – All Clinical and Challenge Isolates

Organism	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher	Eval.	Non-eval.
S. aureus	0	13	163	50	0	226	0
		5.8%	72.1%	22.1%[a]			
E. faecalis	0	1	93	34	3	131	0
		0.8%[b]	71%	26.0%	2.3%		

[a] Difference: -6.3, 95% CI (-22.68% to -10.13%)
[b] Difference: -25.2, 95% CI (-35.75% to -19.68%)

The trending towards higher MIC values and the potential for occurrence of major errors for Tedizolid when testing *S. aureus* (both MSSA and MRSA) and *E. faecalis* isolates was addressed in the labeling by adding the following footnote:

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

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. Interpretive Criteria for Tedizolid (FDA Drug Label)

Organism	FDA Interpretive Criteria for Tedizolid MIC (µg/mL)		
	S	I	R
S. aureus (including MRSA)	≤ 0.5	1	≥2
E. faecalis	≤ 0.5	--	--

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.