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

A. 510(k) Number:

K153569

B. Purpose for Submission:

To obtain a substantial equivalence determination for Liofilchem MIC Test Strip (MTS) – Dalbavancin at 0.002 – 32 µg/mL for susceptibility testing of *Staphylococcus aureus (*including methicillin resistant strains) and *Enterococcus faecalis* (vancomycin susceptible strains).

C. Measurand:

Dalbavancin 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) – Dalbavancin at 0.002 – 32 µg/mL

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   II

3. Product code:

   JWY

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 purpose of the 510(k) is specifically for the dalbavancin MTS at concentrations of 0.002 – 32 µg/mL interpreted after 24 hours of incubation.

   Dalbavancin has been shown to be active against the following bacteria, both clinically and in vitro according to the FDA label:

   Staphylococcus aureus (including methicillin resistant strains)

   Enterococcus faecalis (vancomycin susceptible strains only)

3. Special conditions for use statement(s):

   For prescription use

   The following limitation is included in the device labeling:

Limitation: *Results obtained with MRSA and dalbavancin have shown potential very major discrepancies when compared to the reference method due to a lack of interpretive categories other than susceptible. To avoid potential very major discrepancies, testing should be repeated using an alternative/reference method prior to reporting results when the MIC is 0.25 µg/mL.*

4. Special instrument requirements:

   Manual reading only.

I. Device Description:

The Liofilchem MIC Test Strip (MTS) is made of special high quality paper impregnated with a predefined concentration gradient of dalbavancin, across 15 two-fold dilutions like those of a conventional MIC method. One side of the strip is labelled with the dalbavancin code (DAL) 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):

   Etest® Ceftaroline

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

   K121002

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	**Device Liofilchem MTS Dalbavancin**	**Predicate Etest® Ceftaroline K121002**
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Media	Mueller Hinton Agar	Same
Inoculation	Isolated colonies from culture in suspension equivalent to a 0.5 McFarland standard. Inoculum is manually applied to the agar with a swab.	Same
Result	MIC	Same
Reading	Manual; the point at which the edge	Same

Similarities		
Item	**Device Liofilchem MTS Dalbavancin**	**Predicate Etest® Ceftaroline K121002**
	of the inhibition ellipse intersects the MIC Test Strip	
Incubation	35° C ± 2° C for 16 – 20 hours	Same

Differences		
Item	**Device Liofilchem MTS Dalbavancin**	**Predicate**
Strip Material	Special high quality paper	Plastic
Antimicrobial Agent	Dalbavancin	Ceftaroline

K. Standard/Guidance Document 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-S25 "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement, January 2015"

L. Test Principle:

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 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. 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:

Testing using the Liofilchem MIC Test Strip (MTS) – Dalbavancin was performed using ten isolates of *S. aureus* (two isolates of MSSA and eight isolates of MRSA) and ten isolates of *E. faecalis*. Testing was performed at three sites in triplicate on three separate days to

determine site to site reproducibility. All results for both *S. aureus* and *E. faecalis* were within ± one doubling dilution compared to the mode MIC value; there were no off-scale results. The results were acceptable and demonstrated ≥ 95% reproducibility.

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 with both the Liofilchem MTS – Dalbavancin and the reference method. Results demonstrate that the device can produce QC results in the recommended ranges (Table 2).

Table 2. Quality Control Test Results for Dalbavancin

Organism	Concentration	Reference Method	Liofilchem Dalbavancin
S. aureus ATCC®29213	<0.03	-	-
	0.03	5	-
	0.06	34	64
Expected Range 0.03 – 0.12 µg/mL	0.12	21	13
	> 0.12	-	-
E. faecalis ATCC® 29212	<0.03	-	-
	0.03	20	-
	0.06	30	34
Expected Range 0.03 – 0.12 µg/mL	0.12	10	43
	>0.12	-	-

Organism suspensions were prepared using a validated nephelometer. Colony counts were performed from suspensions made with QC isolates, reproducibility isolates, and a portion of the clinical and challenge isolates for both *S. aureus* and *E. faecalis*. Results demonstrated that the inocula were in the acceptable range.

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 performed at three sites and included 311 isolates of *S. aureus* (156 MSSA strains and 155 MRSA strains), and 319 vancomycin susceptible *E. faecalis* isolates. All *S. aureus* and *E. faecalis* testing provided evaluable MIC values. The majority of the clinical isolates were fresh isolates (56.9% and 65.8% of *S. aureus* and *S. faecalis*, respectively, tested within one week of isolation); the remainder were recent isolates (tested within one year of isolation).

A total of 152 challenge isolates were tested. The challenge isolates included 76 *S. aureus* strains (10 strains of MSSA and 66 strains of MRSA). Seventy four of the 76 *S. aureus* isolates provided evaluable MIC values. A total of 76 *Enterococcus* species challenge isolates were tested including 39 challenge strains of *E. faecalis.* Even though Dalbavancin is not indicated for *E. faecium*, this organism was used to evaluate the ability of the Liofilchem MTS – Dalbavancin to detect resistance in enterococci since the occurrence of resistance in *E. faecalis* is rare. An additional 37 strains of *E. faecium* were also tested. Thirty-one of 39 *E. faecalis* isolates and 15/37 *E. faecium* isolates provided evaluable MIC values.

Results obtained with Liofilchem MTS - Dalbavancin were compared to results obtained with frozen reference MIC panels prepared with 0.002% polysorbate-80 as outlined in CLSI document M100-S25. Reference panel MIC values were interpreted as outlined in CLSI document M7-A10.

Isolated colonies from an overnight blood agar plate were suspended in saline to create a suspension approximating a 0.5 McFarland turbidity standard (approximately10^8 CFU/mL); the suspension turbidity was confirmed using a validated nephelometer. At two sites Mueller Hinton agar was inoculated manually using a swab, at one site plates were inoculated using a plate rotator. There was no difference in performance for the site using the plate rotator to inoculate the plate as compared to sites using the manual plate inoculation method. The inoculated Mueller Hinton agar plates were incubated in an inverted position at 35°C ±2 for 16 to 20 hours.

The results from clinical and challenge testing with *S. aureus* demonstrated a combined EA of 100% and CA of 97.4% (Table 3). Seven challenge isolates of MRSA gave MIC values of 0.5 µg/mL (non-susceptible) by the reference method but gave Liofilchem MTS – Dalbavancin results of 0.25 µg/mL (susceptible), potential very major errors. Because of the current lack of interpretive categories other than susceptible (i.e., no intermediate and resistant breakpoints) for this antimicrobial agent, and because all results are within essential agreement with the reference method, these results are considered acceptable and the following footnote to the performance table and limitation were added to the device labeling:

Footnote to the performance table: *Seven of 11 MRSA isolates that were non-susceptible by the reference method (0.5 µg/mL) gave susceptible results (0.25 µg/mL) with MTS-Dalbavancin, potential very major discrepancies.*

Limitation: *Results obtained with MRSA and dalbavancin have shown potential very*

major discrepancies when compared to the reference method due to the lack of interpretive categories other than susceptible. To avoid potential very major discrepancies, testing should be repeated using an alternative/reference method prior to reporting results when the MIC is 0.25 µg/mL.

One clinical isolate of MSSA and two challenge isolates of MRSA had MIC values of 0.25 µg/mL by the reference method but gave Liofilchem MTS-Dalbavancin results of 0.5 µg/mL (Table 3). These results represent potential major errors. These major errors contributed to an overall potential major error rate of 0.8% which is within the acceptable range.

Table 3. Performance of Clinical and Challenge *S. aureus* Isolates

	Tot	No. EA[a]	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS[b]	min	maj	vmj
Clinical MRSA	155	155	100	155	155	100	155	100	0	NA	NA	NA
Challenge MRSA	66	66	100	65	65	100	57	86.4	17	NA	NA	NA
Total MRSA	221	221	100	220	220	100	212	95.9	17	NA	NA	NA
Clinical MSSA	156	156	100	156	156	100	155	99.4	1	NA	NA	NA
Challenge MSSA	10	10	100	9	9	100	10	100	4	NA	NA	NA
Total MSSA	166	166	100	165	165	100	165	99.4	5	NA	NA	NA
Combined MRSA and MSSA	387	387	100	385	385	100	377	97.4	22	NA	NA	NA

[a] Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of Liofilchem MTS Dalbavancin within ± one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the Liofilchem MTS Dalbavancin and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of Liofilchem MTS Dalbavancin.

EA – Essential Agreement (+/- 2 dilutions)
CA – Category Agreement
EVAL – Evaluable isolates
R or NS – Resistant or non-susceptible isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

[b] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for additional testing.

The results from clinical and challenge testing with *E. faecalis* demonstrated a combined EA of 99.7% and CA of 100.0% (Table 4).

Table 4. Performance of Clinical and Challenge *E. faecalis* Isolates and Challenge Isolates of *E. faecium*

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS[a]	min	maj	vmj
Clinical *E. faecalis*	319	318	99.7	319	318	99.7	319	100	0	NA	NA	NA
Challenge *E. faecalis*	39	39	100	31	31	100	39	100	9	NA	NA	NA
Clinical and Challenge *E. faecalis* Combined	358	357	99.7	350	349	99.7	358	100	9	NA	NA	NA
Challenge *E. faecium*	37	36	97.3	15	14	93.3	37	100	29	NA	NA	NA

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for additional testing.

Trending

There was no significant trending noted with isolates of *S. aureus*. However, 44.7% of the 358 clinical and challenge *E. faecalis* isolates gave MIC values one doubling dilution higher than the reference method (Table 5); one isolate (0.2%) gave an MIC value two doubling dilutions higher than the reference method. The following footnote was added to the device labeling:

> **Footnote**: *The dalbavancin MTS MIC values tended to be one doubling dilution higher when testing E. faecalis compared to the reference broth microdilution (out of 358 E. faecalis isolates tested, 2.2% were 1 dilution lower, 52.8% were equivalent, 44.7% were 1 dilution higher and 0.3% were 2 dilutions higher compared to the CLSI broth microdilution results.)*

Table 5. Trending of *E. faecalis* with Liofilchem MTS-Dalbavancin

Organism	No. strains	Difference in MIC as Compared to the CLSI Reference Method			
		-1	0	+1	+2
Clinical	319	8	165	146	1
Challenge	39	-	24	15	
Total	358	8 (2.2%)	189 (52.8%)	160 (44.7%)	1 (0.2%)

b. Matrix comparison:

Not applicable

3. Clinical studies:

   a. Clinical Sensitivity:

   Not applicable

   b. Clinical specificity:

   Not applicable

   c. Other clinical supportive data:

   Not applicable

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

Table 6. FDA Breakpoints and Interpretive Categories for Dalbavancin

Organisms	MIC (µg/mL)[a]		
	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.25	-	-
Enterococcus faecalis (vancomycin susceptible isolates only)	≤ 0.25	-	-

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for additional testing.

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.