Food and Drug Administration
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510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K191908

B Applicant

Liofilchem s.r.l.

C Proprietary and Established Names

MTS Imipenem 0.016-256 µg/mL

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for Imipenem at concentrations of 0.016 – 256 µg/mL for susceptibility testing of non-fastidious Gram-negative organisms

B Measurand:

Imipenem 0.016 – 256 µg/mL

C Type of Test:

Quantitative Antimicrobial Susceptibility Test growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

MTS (MIC Test Strip) Imipenem 0.016-256 μg/mL 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.

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

Imipenem has been shown to be active both clinically and in vitro against these bacterial species according to the FDA drug approved label:

Gram-negative bacteria:
Citrobacter freundii
Citrobacter koseri
Enterobacter asburiae
Enterobacter cloacae
Escherichia coli
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Serratia marcescens
Acinetobacter baumannii
Pseudomonas aeruginosa

Imipenem has been shown to be active in vitro only against the non-fastidious bacteria listed below according to the FDA drug approved label:

Gram-negative bacteria:
Providencia stuartii

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The ability of the 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.
Imipenem: *Providencia stuartii*

D Special Instrument Requirements:

N/A

IV Device/System Characteristics:

A Device Description:

The MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of Imipenem across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. One side of the strip is labelled with the imipenem code (IMI) and the MIC reading scale in µg/mL. MIC values are determined by identifying the drug concentration at which growth of the ellipse ends.

B Principle of Operation:

MTS are made of specialized paper impregnated with a predefined concentration gradient of antibiotic, across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. 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 0.125 µg/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.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Liofilchem MIC Test Strip (MTS) -Vancomycin 0.016 -256 ug/mL

B Predicate 510(k) Number(s):
K153687

C Comparison with Predicate(s):

Table 1: Comparison with Predicate (K153687)

Device & Predicate Device(s):	**K191908**	**K153687**
Device Trade Name	**Liofilchem MTS, Imipenem**	**Liofilchem MTS, Vancomycin**
General Device Characteristic Similarities		
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
Result	MIC	Same
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip; interpret the MIC at 100% inhibition	Same
General Device Characteristic Differences		
Intended Use/Indications For Use	Quantitative susceptibility to antimicrobial agents against non-fastidious Gram-negative organisms	Quantitative susceptibility to antimicrobial agents against Gram-positive organisms
Antibiotic	Imipenem (IMI)	Vancomycin (VA)
Drug Concentration Range	0.016 – 256 µg/mL	0.016 -256 µg/mL
Incubation	35 ± 2°C for 16 – 20 hours	35 ± 2°C for 24 hours

VI Standards/Guidance Documents Referenced:

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

- CLSI M07-A10 *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard*, Tenth Edition January 2015.
- CLSI M100-29th ed. *Performance Standards for Antimicrobial Susceptibility Testing* (January 2019).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites using 10 Gram-negative organisms. Each isolate was tested in triplicate over three days for a total of 270 data points. The mode of MIC values was determined for each isolate and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode. The Gram-negative reproducibility panel included two *E. coli*, one *K. pneumoniae*, one *K. oxytoca*, one *K. aerogenes*, one *E. cloacae*, one *P. mirabilis*, one *A. baumannii*, and two *P. aeruginosa* isolates. All MIC results were on scale. The testing resulted in overall reproducibility of greater than 95%. The results were acceptable.

2. Linearity:

   N/A

3. Analytical Specificity/Interference:

   N/A

4. Assay Reportable Range:

   N/A

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Inoculum Density Check:
   The inoculum was prepared to achieve turbidity equivalent to a 0.5 McFarland standard. Colony counts were performed periodically at each site for all QC replicates, from at least one replicate of each reproducibility isolate on each of the three days of testing, and from a minimum of 10% of the clinical and challenge strains tested. Inoculum density checks were performed, and the colony counts obtained for each isolate were within the recommended range of approximately 1×10^8 CFU/mL.

   Purity Checks:
   Purity checks were performed on all isolates following MTS inoculation. All isolates were pure in both the broth microdilution reference panels and the MTS agar plates.

   Growth Failure Rate:
   None of the isolates in the study failed to grow with the Imipenem MTS.

Quality Control (QC) Testing:
The recommended CLSI QC strains, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853, for testing imipenem were tested at three sites for a minimum of 20 times at each site by both the MTS and the reference method. The results demonstrate that the imipenem MTS can produce quality control results in the recommended range >95% of the time (Table 2).

Table 2: Quality Control Summary for Imipenem with the CLSI-Recommended QC Strain

QC Organism	Imipenem Expected Range (µg/mL)	Concentration (µg/mL)	Reference (All sites)	MTS (All sites)
E. coli ATCC 25922	0.06 – 0.25 µg/mL	0.03		
		0.06		1
		0.12	51	3
		0.25	11	58
		0.5		
P. aeruginosa ATCC 27853	1 – 4	0.5		
		1	7	1
		2	53	39
		4	2	22
		8		

6. Detection Limit:

   N/A

7. Assay Cut-Off:

   N/A

B Comparison Studies:

1. Method Comparison with Predicate Device:

The MTS, Imipenem was evaluated at three sites located within the United States. Each clinical isolate was tested one time by MTS Imipenem and the reference method using the same initial standardized suspension. A total of 467 non-fastidious Gram-negative isolates were tested of which 61.9% were tested within six months of isolation (contemporary isolates). The indicated Gram-negative organisms that were tested for imipenem included 30 *C. freundii*, 9 *C. koseri*, 8 *E. asburiae*, 31 *E. cloacae*, 75 *E. coli*, 30 *K. aerogenes*, 30 *K. oxytoca*, 60 *K. pneumoniae*, 12 *M. morganii*, 15 *P. vulgaris*, 15 *P. rettgeri*, 15 *P. stuartii*, 15 *S. marcescens*, 60 *P. aeruginosa*, and

47 *A. baumannii* isolates. The sponsor also tested 15 *P. mirabilis* isolates as non-indicated isolates.

Challenge testing was performed at one internal site. A total of 76 Gram-negative challenge isolates were tested. The Gram-negative organisms included 3 *C. freundii*, 2 *C. koseri*, 11 *E. cloacae*, 8 *E. coli*, 6 *K. aerogenes*, 2 *K. oxytoca*, 11 *K. pneumoniae*, 2 *M. morganii*, 2 *P. mirabilis*, 2 *P. vulgaris*, 2 *P. rettgeri*, 2 *P. stuartii*, 3 *S. marcescens*, 14 *P. aeruginosa*, and 6 *A. baumannii* isolates.

Results obtained with the MTS Imipenem were compared to results obtained with the CLSI broth microdilution reference panel. The reference panel contained two-fold serial dilutions of Imipenem with a range of 0.016 – 256 μg/mL. The testing conditions for the reference method were consistent with CLSI guidelines as listed in the CLSI document M07-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 an inverted position at 35°C ± 2° for 16-20 hours. At the end of incubation, the MIC value determined at 100% inhibition of growth along the strip was compared to MIC results obtained with the reference method. Visual aids were provided in reading guides to each laboratory to assist in interpretation.

The performance (combined clinical and challenge) for the 416 *Enterobacteriaceae*, 74 *P. aeruginosa*, and 53 *A. baumannii* isolates is summarized in Tables 3, 4, and 5 below. To address testing and reporting of non-indicated species, the sponsor included the following statement in the Precautions section of the device labeling:

> *Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

Table 3: Overall Performance of *Enterobacteriaceae* Clinical and Challenge Isolates

Imipenem	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
Enterobacteriaceae Clinical	360	346	96.1	358	344	96.1	332	92.2	82	28	0	0
Challenge	56	56	100	50	50	100	54	96.4	43	2	0	0
Combined	416	402	96.6	408	394	96.6	386	92.8	125	30	0	0

Table 4: Overall Performance of *P. aeruginosa* Clinical and Challenge Isolates

Imipenem	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
P. aeruginosa Clinical	60	60	100	58	58	100	58	96.7	19	2	0	0
Challenge	14	14	100	12	12	100	14	100	13	0	0	0
Combined	74	74	100	70	70	100	72	97.3	32	2	0	0

Table 5: Overall Performance of *Acinetobacter baumannii* Clinical and Challenge Isolates

Imipenem	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
A. baumannii Clinical	47	46	97.9	43	42	97.7	45	95.7	29	2	0	0
Challenge	6	6	100	3	3	100	6	100	6	0	0	0
Combined	53	52	98.1	46	45	97.8	51	96.2	35	2	0	0

EA – Essential agreement
CA – Category agreement
Eval. – Evaluable isolates
R – Resistant isolates
maj – Major errors
vmj – Very major errors
min – Minor errors

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.

An insufficient number of resistant strains were evaluated for *P. stuartii*. As such, the sponsor included the following limitation in the package insert:

> *The ability of the 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.*
>
> *Imipenem: Providencia stuartii*

The overall performance of indicated *Enterobacteriaceae* isolates (Table 3) including *P. mirabilis* is acceptable with 96.6% EA and 92.8% CA. Excluding *P. mirabilis* (non-indicated), the overall performance remains acceptable at 96.5% EA and 93.2% CA. There were no major or very major errors. When *K. aerogenes*, *M. morganii*, *P. mirabilis*, and *P. vulgaris* were evaluated separately, they all yielded a CA of less than 90% (80.6%, 78.6%, 82.4%, and 82.4%, respectively), however, given that all categorical errors were minor and that the evaluable EA was 100% for these organisms, the performance was considered acceptable. When *P. stuartii* was evaluated separately, the CA was <90% (13/17=76.5%), however, the performance is considered acceptable because the evaluable EA (16/17=94.1%) is acceptable and all categorical errors were minor.

The overall performance of *P. aeruginosa* isolates (Table 4) is acceptable with 100% EA and 97.3% CA. There were no major or very major errors.

The overall performance of *A. baumannii* isolates (Table 5) is acceptable with 98.1% EA and 96.2% CA. There were no major or very major errors.

Enzyme Group Characterization/Resistance Markers Information:

Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* isolates with beta-lactamases were included in the imipenem comparative studies which consisted of the challenge isolates that were tested. Isolates with the following beta lactamases were included: AmpC (4), KPC (8), OXA (11), CTX-M (8), TEM (8), SHV (8), CMY (3), DHA (1), ACT (4), NDM (26), VIM (10), and IMP (6).

Trending:

Trending was assessed separately for Gram-negative organisms using data for challenge and clinical isolates (Tables 6). Trending was assessed using current trending review practices (i.e., ≥30% difference between higher and lower dilution readings). No significant trending was observed for *Enterobacteriaceae* overall; however, trending was observed for *C. koseri, E. asburiae, E. coli, M. morganii,* and *P. aeruginosa* which tended to be in exact agreement or higher when compared to the reference method. Given the observed trending, the following was included in the labeling:

> *Liofilchem MIC Test Strip (MTS) Imipenem MIC values tended to be in exact agreement or at least one doubling dilution higher when testing C. koseri, E. asburiae, E. coli, M. morganii, and P. aeruginosa compared to the CLSI reference broth microdilution.*

Table 6: Imipenem Trending Analysis for Gram-Negative Organisms

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
C. freundii	**33**	**6 (18.2)**	**19 (57.6)**	**8 (24.2)**	**6.1 (-13.76-25.4)**	**No**
C. koseri	**11**	**0**	**3 (27.3)**	**8 (72.7)**	**72.7 (33.6-90.2)**	**Yes**
E. asburiae	**8**	**0**	**4 (50)**	**4 (50)**	**50 (6.8-78.5)**	**Yes**
E. cloacae	**39**	**5 (12.8)**	**18 (46.2)**	**16 (41)**	**28.2 (8.5-43.4)**	**No**
E. coli	**83**	**3 (3.6)**	**29 (34.9)**	**51 (61.5)**	**57.8 (45.3-67.9)**	**Yes**
K. aerogenes	**36**	**8 (22.2)**	**23 (63.9)**	**4 (11.1)**	**-11.11 (-28.3-6.6)**	**No**
K. oxytoca	**32**	**7 (21.9)**	**12 (37.5)**	**13 (40.6)**	**18.8 (-3.9-39)**	**No**
K. pneumoniae	**71**	**29 (40.1)**	**20 (28.2)**	**22 (31)**	**-9.86 (-24.9-5.8)**	**No**
M. morganii	**14**	**0**	**8 (57.1)**	**6 (42.9)**	**42.9 (12.5-67.4)**	**Yes**
P. vulgaris	**17**	**4 (23.5)**	**13 (76.5)**	**0**	**-23.5 (-47.3--0.4)**	**No**
P. rettgeri	**17**	**1 (5.9)**	**14 (82.4)**	**2 (11.8)**	**5.9 (-16.9-29)**	**No**
P. stuartii	**17**	**1 (5.9)**	**12 (70.6)**	**4 (23.5)**	**17.7 (-7.7-41.9)**	**No**

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
S. marcescens	**18**	**6 (33.3)**	**11 (61.1)**	**1 (5.6)**	**-27.8 (-51.2- -1.3)**	**No**
Enterobacteriaceae	**413**	**72 (17.4)**	**199 (48.2)**	**142 (34.4)**	**17 (11-22.7)**	**No**
P. aeruginosa	**70**	**2 (2.9)**	**37 (52.9)**	**31 (44.3)**	**41.4 (28.4-53.2)**	**Yes**
A. baumannii	**52**	**11 (21.2)**	**15 (30.8)**	**25 (48.1)**	**26.9 (8.6-42.9)**	**No**

2. Matrix Comparison:

N/A

C Clinical Studies:

1. Clinical Sensitivity:

N/A

2. Clinical Specificity:

N/A

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

N/A

D Clinical Cut-Off:

N/A

E Expected Values/Reference Range:

The FDA-identified susceptibility interpretive criteria for imipenem are as listed in Table 7.

Table 7: FDA-Recognized Interpretive Criteria[a] for Imipenem (µg/mL)

	Susceptible (S)	Intermediate (I)	Resistant (R)
Enterobacteriaceae	≤1	2	≥4
P. aeruginosa	≤2	4	≥8
A. baumannii	≤2	4	≥8

[a] FDA STIC Webpage https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that Liofilchem intends to use to evaluate the Liofilchem MIC test strip (MTS) when revised breakpoints for imipenem are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Liofilchem will update the imipenem device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.