

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

A. 510(k) Number:

K141651

B. Purpose for Submission:

To obtain a substantial equivalence determination by demonstrating acceptable performance of the Sensititre HP MIC or Breakpoint Susceptibility Test System with the revised CLSI and FDA interpretive criteria (breakpoints) for Telavancin and *Streptococcus* spp., utilizing the 0.002% Polysorbate 80 for the reference method.

C. Measurand:

Telavancin in the dilution range of 0.0005-2µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST), growth based fluorescence.

E. Applicant:

Trek Diagnostic Systems, Inc.,

F. Proprietary and Established Names:

Sensititre Susceptibility Plates

G. Regulatory Information:

1. Regulation section:

21 CFR 866.1640 Antimicrobial Test Powder

2. Classification:

Class II

3. Product code(s):

JWY – Manual Antimicrobial Susceptibility Test Systems

LRG – Instrument for Auto Reader & Interpretation of overnight suscept systems

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

83 - Microbiology

H. Intended Use:

1. Intended use(s):

The Sensititre HP MIC Susceptibility plate is an in vitro diagnostic product for clinical susceptibility testing of fastidious isolates.

2. Indication(s) for use:

The Sensititre HP MIC Susceptibility plate is an in vitro diagnostic product for clinical susceptibility testing of fastidious isolates.

This 510 (k) is for the newly approved breakpoints for Telavancin, utilizing the 0.002% Polysorbate 80 for the reference method in the dilution range of 0.0005-2µg/mL to the Sensititre HP MIC Susceptibility plate for testing *Streptococcus* spp.

The approved primary “Indications for Use” and clinical significance for *Streptococcus* spp. is for the following species:

Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus anginosus

3. Special conditions for use statement(s):

Prescription use only.

The ability of the Sensititre system to detect non-susceptible isolates to Telavancin is unknown because non-susceptible isolates were not available at the time of the comparative testing. If such isolates are observed, they should be submitted to a reference lab.

4. Special instrument requirements:

The Sensititre Autoinoculator/AIM™, the Sensititre Optiread™/Autoreader, the Sensititre Vizion® and the Sensititre Nephelometer.

I. Device Description:

Each plate is dosed with antimicrobial agents at appropriate dilutions. Results can be read manually by visual reading of growth or automatically on an ARIS® / Autoreader® / OptiRead® using fluorescence. The Sensititre Autoreader/OptiRead® system utilizes fluorescence technology. The technology involves the detection of bacterial growth by monitoring the activity of specific surface enzymes produced by the test organism. Growth is determined by generating a fluorescent product from a non-fluorescent (fluorogenic) substrate. The non-fluorescent substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond, which prevents fluorescence. The fluorophore is then said to be quenched. The plates are prepared with the substrate already added to the plate. Enzymatic action of the bacterial surface enzymes on the specific substrates cleaves this bond releasing the fluorophore, which is now capable of fluorescence. The amount of fluorescence detected is directly related to the activity of the bacterial surface enzymes and, therefore, to the bacterial growth.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Sensititre® HP MIC Susceptibility Plate Telavancin 0.001-2 µg/mL and The Sensititre® 18-24 hour MIC Susceptibility System Susceptibility Test Panel for Telavancin 0.03-16 µg/mL

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

k093865

3. Comparison with predicate:

Table 1. Similarities and Differences of the Sensititre 20-24 hour and the Predicate

Similarities		
Item	Device	Predicate
Intended Use	The Sensititre MIC or Breakpoint Susceptibility system is an <i>in vitro</i> diagnostic product for clinical susceptibility testing	Same
Test Panel	Each 96 well plate is precision dosed with selected	Same

Similarities		
Item	Device	Predicate
	antimicrobial agents and substrate for the fluorescent reads, then dried. The bacterial suspension in the appropriate broth is used to rehydrate the plate	
Instrumentation	Each plate is dosed with antimicrobial agents at appropriate dilutions and inoculated with standardized organism suspension. Results can be read automatically on ARIS [®] /Autoreader [®] /OptiRead [®] using fluorescence or manually on the Vizion or a manual viewer, by visual reading of growth.	Same
Reading method	Fluorescence	Same

Differences		
Item	Device	Predicate
Antibiotic/Assay	Telavancin, New Breakpoints: <i>Streptococcus pyogenes</i> and <i>Streptococcus agalactiae</i> ≤ 0.12 <i>Streptococcus anginosus</i> group ≤ 0.06	Telavancin, Old Breakpoints K093865: <i>S. aureus</i> ≤1 <i>E. faecalis</i> ≤1 <i>S. pyogenes</i> ≤0.12 <i>S. agalactiae</i> ≤0.12 <i>S. anginosus</i> group ≤0.12
Product Name	Sensititre™ 20-24 hour Susceptibility System Sensititre Haemophilus/ <i>Streptococcus</i> <i>pneumoniae</i> (HP) MIC Susceptibility Plates	Sensititre™ 18-24 hour Susceptibility System Sensititre Haemophilus/ <i>Streptococcus</i> <i>pneumoniae</i> (HP) MIC Susceptibility Plates
Test Organism	fastidious gram positive isolates, <i>Streptococcus</i> spp.	Non-fastidious gram positive isolates & fastidious gram positive isolates, <i>Streptococcus</i> spp.
Incubation	20-24 hours for non-fastidious	18-24 hours for non- fastidious and 20-24 hours for fastidious
Reference Method	CLSI (with 0.002% Polysorbate 80)	CLSI (without 0.002% Polysorbate 80)
Quality Control organisms and ranges for Telavancin	<i>Streptococcus pneumoniae</i> ATCC 49619 (0.004-0.015 µg/mL)	<i>Streptococcus pneumoniae</i> ATCC 49619 (0.004-0.006 µg/mL)

Differences		
Item	Device	Predicate
		<i>S. aureus</i> ATCC 29213 (0.12-1 µg/mL) <i>E. faecalis</i> ATCC 29212 (0.12-0.5 µg/mL)
Telavancin Dilution range	0.0005-2 µg/mL	0.001 to 16 µg/mL The MIC testing and reporting result range is 0.001-2 µg/mL for <i>Streptococcus</i> spp and 0.03-16 µg/mL for other Gram positive isolates.

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

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucmO71462.pdf>
2. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard-9th Edition, Document M07-A9
3. Performance Standards for Antimicrobial Susceptibility Testing - 24th Informational Supplement, M100-S24.

L. Test Principle:

Sensititre susceptibility plates are multi-well plastic microtiter plates that contain doubling dilutions of antibacterial agents. Each plate is dosed with antimicrobial agents at appropriate dilutions. Results can be read manually by visual reading of growth or automatically on an Autoreader[®] using fluorescence. The Sensititre Autoreader system utilizes fluorescence technology which involves the detection of bacterial growth by monitoring the activity of specific surface enzymes produced by the test organism. Growth is determined by generating a fluorescent product from a non-fluorescent (fluorogenic) substrate. The substrate can be added to the inoculum broth and dispensed into the test plates at the same time as the test organism or the plates can be prepared with the substrate already added to the plate. The nonfluorescent substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond, which prevents fluorescence (i.e. the fluorophore is quenched in this state). Enzymatic action of the bacterial surface enzymes on the specific substrates cleaves this bond releasing the fluorophore which is now capable of fluorescence. The amount of fluorescence detected is directly related to the activity of the bacterial surface enzymes and, therefore, to bacterial growth.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A reproducibility study was conducted at three study sites. Twenty five *Streptococcus* spp were tested at each site (One *S. anginosus*, 11 *S. pyogenes*, 13 *S. agalactiae*) on the Sensititre HP MIC Susceptibility Plates which were read manually and automatically (20-24 hours).

Results were read automatically (using the AutoReader) and manually (using the Vizion).

Reproducibility was calculated as the percent of results for the combined sites which were within +/- one doubling dilution of the mode MIC value for all sites.

For the sake of reproducibility calculations, off-scale values are handled in two ways; "best case" and "worst case" scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value. There were no off-scale results in this study. So, only one value for overall reproducibility is reported for each reading method.

The overall reproducibility was 100% for *Streptococcus* spp read manually (Vizion) and automatically (AutoReader).

b. *Linearity/assay reportable range:*

Not applicable

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

The FDA and CLSI recommended QC isolates were tested on every test occasion with the reference method and the Sensititre HP MIC Susceptibility Plates. The reference method QC results were in range for every day tested. The Sensititre Susceptibility plate was tested a sufficient number of times to demonstrate that the system can produce QC results in the recommended range.

Quality Control was performed at all sites during the studies using both the AutoReader and the manual reading method (Vizion). The mode of the MIC obtained by the Sensititre manual read was similar to that obtained by the AutoReader. Summary of the results are shown in table 2 below.

Table 2. Summary of Quality Control Results for Telavancin for Fastidious Organisms

ORGANISMS	Telavancin (µg/mL)	Reference	AutoReader	Manual Read
<i>S. pneumoniae</i> ATCC 49619 0.004-0.015 µg/mL	0.002			
	0.004	5	5	9
	0.008	45	49	41
	0.015	10	6	10
	0.03			

Quality Control results for the Sensititre Susceptibility System using either reading methods demonstrated that the system could produce the expected quality control results.

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:

Performance was established through a clinical study which was conducted at three sites. Studies have been conducted with the Sensititre dried susceptibility plates containing Telavancin to test susceptibility of *Streptococcus* spp. (Sensititre *Streptococcus* spp. HP MIC plate). The CLSI microdilution reference methods with 0.002% Polysorbate 80 containing the same antimicrobial in the same dilutions were used for a comparison and evaluation of performance.

The inoculum was prepared using the Sensititre Nephelometer which was calibrated at the start of each test. Plates were inoculated and incubated at 35° C. The reading was done automatically on the AutoReader and manually using the Vizion at 20-24 hours.

For the manual read, clinical testing was performed on 372 *Streptococcus* spp (165 *Streptococcus pyogenes*, 165 *Streptococcus agalactiae* and 42 *Streptococcus anginosus*).

For the Auto Read, clinical testing was performed on 371 *Streptococcus* spp. (164 *Streptococcus pyogenes*, 165 *Streptococcus agalactiae* and 42 *Streptococcus anginosus*). All were freshly collected clinical isolates. In addition, testing was performed on 60 *Streptococcus* spp. stock challenge isolates (25 *Streptococcus pyogenes*, 25 *Streptococcus agalactiae* and 10 *Streptococcus anginosus*) for both Auto Read and manual Read. The performance evaluations are shown in table 3 and 4 below.

Table 3. Trek Telavancin Summary Table for fastidious organisms (AutoReader)

	EA TOT	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	No. NS	min	maj	vmj
<i>Streptococcus pyogenes</i>												
Clinical	164	162	98.8	164	162	98.8	164	100	0	0	0	0
Challenge	25	24	96	25	24	96	25	100	0	0	0	0
Combined	189	186	98.4	189	186	98.4	189	100	0	0	0	0
<i>Streptococcus agalactiae</i>												
Clinical	165	164	99.4	165	164	99.4	164	99.4	0	0	1	0
Challenge	25	24	96	25	24	96	25	100	0	0	0	0
Combined	190	188	98.9	190	188	98.9	189	99.5	0	0	1	0
<i>Streptococcus anginosus</i> grp (<i>S. anginosus</i> , <i>S. intermedius</i> , and <i>S. constellatus</i>)												
Clinical	42	40	95.2	41	40	97.6	42	100	0	0	0	0
Challenge	10	10	100	10	10	100	10	100	0	0	0	0
Combined	52	50	96.2	51	50	98	52	100	0	0	0	0

Table 4. Trek Telavancin Summary Table for fastidious organisms (Manual Read)

	EA TOT	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	No. NS	min	maj	vmj
<i>Streptococcus pyogenes</i>												
Clinical	165	162	98.2	165	162	98.2	165	100	0	0	0	0
Challenge	25	25	100	25	25	100	25	100	0	0	0	0
Combined	190	187	98.4	190	187	98.4	190	100	0	0	0	0
<i>Streptococcus agalactiae</i>												
Clinical	165	165	100	165	165	100	165	100	0	0	0	0
Challenge	25	25	100	25	25	100	25	100	0	0	0	0
Combined	190	190	100	190	190	100	190	100	0	0	0	0
<i>Streptococcus anginosus</i> group (<i>S. anginosus</i> , <i>S. intermedius</i> , and <i>S. constellatus</i>)												
Clinical	42	42	100	42	42	100	42	100	0	0	0	0
Challenge	10	10	100	10	10	100	10	100	0	0	0	0
Combined	52	52	100	52	52	100	52	100	0	0	0	0

EA-Essential Agreement

CA-Category Agreement

NS-not susceptible

Essential agreement (EA) is when the Sensititre panels agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the Sensititre panel result interpretation agrees exactly with the reference panel result interpretation. Evaluable EA is when the MIC result is on scale for both the Sensititre and the reference and have on-scale EA.

The EA% is acceptable when compared to the reference method as described in the FDA guidance document, "Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA".

Currently, there are no intermediate or resistance interpretive criteria for Telavancin. There were no minor, major or very major errors using the Manual Read Method. However, there was one major error (i.e. susceptible by reference, non-susceptible by the AutoRead) with *S. agalactiae*. As summarized in table 5 below, the combined (clinical + challenge).

Table 5. Performance of Sensititre Panels read manually on the Vizion and on the AutoReader

ORGANISMS	Number of isolates tested	% EA	% CA
Auto Read			
<i>Streptococcus spp. MHB with LHB</i>	431	98.4	99.8
Manual Read Method-Vizion			
<i>Streptococcus spp. MHB with LHB</i>	432	99.3	100

EA and CA for all organisms were greater than 90%.

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.

The trending observed in the overall performance of *S. agalactiae* demonstrates a statistically significant trend towards higher reading in both manual and auto read compared to the CLSI broth micro-dilution method, which raises concerns for potential major errors as summarized in Table 6 below.

Table 6. MIC Trends for *S. agalactiae*

Organism (Reading Method)	# of isolates tested	# on-scale MIC values	% minus two dilution	% minus one dilution	% equal to the reference	% higher one dilution
<i>S. agalactiae</i> (Auto Read)	190	190	NA	18.9 (36/190)	49.5 (94/190)	31.6 (60/190)
<i>S. agalactiae</i> (Manual Read)	190	190	NA	11.1 (21/190)	41.6 (79/190)	47.4 (90/190)

S. pyogenes and *S. anginosus* demonstrates a statistically significant trend towards lower reading in the auto read compared to the CLSI broth micro-dilution method, which raises concerns for potential very major error as summarized in Table 7 below.

Table 7. MIC Trends for *S. pyogenes* and *S. anginosus*

Organism (Reading Method)	# of isolates tested	# on-scale MIC values	% minus two dilution	% minus one dilution	% equal to the reference	% higher one dilution
<i>S. pyogenes</i> (Auto Read)	189	189	NA	32.8 (62/189)	50.8 (96/189)	16.4 (31/189)
<i>S. anginosus</i> (AutoRead)	52	51	1.9 (1/51)	43.1 (20/51)	56.9 (29/51)	1.9 (1/51)

To address this trending issue, the sponsor was requested to add the following footnote to the addendum to technical product Information:

“Sensititre HP Telavancin MIC values for fastidious gram positive organisms tended to be one doubling dilution higher in S. agalactiae and one dilution lower in S. pyogenes and S. anginosus compared to reference broth micro-dilution. Streptococcus spp. with an interpretation of non-susceptible for Telavancin is uncommon in most institutions or may result from technical errors. Verify AST if this phenotype has not been previously encountered from this patient or institution”.

Growth Rate:

The growth rate for the manual and automated read methods was greater than 90%; this meets the acceptance criteria of $\leq 10\%$ non-growth of organisms tested. In the AutoRead method one isolate didn't grow.

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 8. Interpretive Criteria and QC Ranges for Telavancin

Antibiotic/Concentration reviewed	Interpretive Criteria (µg/mL)		
	FDA (S, I, R)	CLSI (S,I,R)	Trek (S, I, R)
Telavancin 0.0005-2 µg/mL			
<i>S. pyogenes</i>	≤0.12,-,-	≤0.12,-,-	≤0.12,-,-
<i>S. agalactiae</i>			
<i>S. anginosus</i> group	≤0.06,-,-	≤0.06,-,-	≤0.06,-,-
QC organism	Expected Range		
<i>S. pneumoniae</i> ATCC 49619	0.004-0.015	0.004-0.015	0.004-0.015

Currently, there are no intermediate or resistance interpretative criteria for Telavancin. The updated pharmaceutical drug label for Telavancin includes interpretive criteria only for susceptible category; therefore, the sponsor was requested to add the following limitation in the Addendum to Technical Product Information:

“The ability of the Sensititre system to detect non-susceptible isolates to Telavancin is unknown because non-susceptible isolates were not available at the time of the comparative testing. If such isolates are observed, they should be submitted to a reference lab”.

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.