

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

A. 510(k) Number:

K140985

B. Purpose for Submission:

Addition of *Streptococcus* species to the Intended Use of Clindamycin (0.015 – 1 µg/mL) in the Sensititre *Haemophilus/Streptococcus pneumoniae* (HP) MIC susceptibility panel.

C. Measurand:

Clindamycin concentrations of 0.015 – 1 µg/mL

D. Type of Test:

Quantitative antimicrobial susceptibility test (AST), growth-based fluorescence

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* MIC Susceptibility Plate

G. Regulatory Information:

1. Regulation section:

21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

Class II

3. Product code:

JWY – Manual Antimicrobial Test

LRG – Instrument for Autoreader and Interpretation of Overnight Susceptibility Systems

LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:

83, Microbiology

H. Intended Use:

1. Intended use(s):

The Sensititre *Haemophilus influenzae*/*Streptococcus pneumoniae* plates are *in vitro* diagnostic products for clinical susceptibility testing of *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus* species.

2. Indication(s) for use:

The Sensititre *Haemophilus influenzae*/*Streptococcus pneumoniae* plates are *in vitro* diagnostic products for clinical susceptibility testing of *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus* species.

This 510(k) is for the addition of Clindamycin in the dilution range of 0.015 – 1 µg/mL to the Sensititre HP MIC Susceptibility plate for testing *Streptococcus* spp. The approved primary “Indications for Use” and clinical significance of Clindamycin is for:

Facultative Gram-Positive Fastidious Microorganisms:

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus anginosus

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

Autoinoculator/AIM only

Manual read (Vizion) or AutoRead (ARIS/AutoReader OptiRead)

I. Device Description:

The Sensititre 18-24 hours MIC Breakpoint Susceptibility System is a micro-version of the classic broth dilutions method and can provide both qualitative and quantitative susceptibility results in a dried microtitre plate format. Each micro-broth dilution plate is dosed with antimicrobial agents at specific dilutions and then dried.

The organism to be tested must be in pure culture and identified as a *Streptococcus* species. A standardized suspension is prepared from colonies in pure growth and inoculated into the microtitre plate using the Sensititre AutoInoculator/AIM instrument (AutoInoculator). After the indicated hours of incubation, the microtitre plate is examined for growth to determine the MIC either manually (Vizion or manual viewer) or using the ARIS/AutoReader/OptiRead (AutoReader). The FDA recommended interpretive criteria for clindamycin are listed in Table 1.

Table 1: FDA interpretive criteria for clindamycin

Organism	Susceptibility Interpretive Criteria (MIC in µg/mL)*†		
	S	I	R
<i>S. pneumoniae</i> , <i>Streptococcus</i> species (<i>S. anginosus</i> , <i>S. pyogenes</i> , <i>S. agalactiae</i>)	≤ 0.25	0.5	≥ 1

* These interpretive standards for *S. pneumoniae* and other *Streptococcus* spp. are applicable only to tests performed by broth microdilution using cation-adjusted Mueller Hinton broth with 2 to 5 % lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35 °C for 20 to 24 hours.

† S, Susceptible; I, Intermediate; R, Resistant

J. Substantial Equivalence Information:

1. Predicate device name(s):

MicroScan MICroSTREP *plus* Panel - Clindamycin

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

K021184

3. Comparison with predicate:

Table 2: Comparison with the predicate device

Similarities		
Item	Device	Predicate
Name	Sensititre <i>Haemophilus/Streptococcus pneumoniae</i> (HP) MIC Susceptibility Plates	MicroScan MICroSTREP plus panel, K021184
Intended Use	Sensititre <i>Haemophilus/Streptococcus pneumoniae</i> (HP) MIC Susceptibility plates is an <i>in vitro</i> diagnostic product for clinical susceptibility testing of <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> and <i>Streptococcus</i> species. This 510(k) is for the addition of clindamycin in the dilution range of 0.015 – 1 µg/mL to the panel.	To determine antimicrobial susceptibility to Clindamycin with aerobic streptococci other than <i>Streptococcus pneumoniae</i> .
Inoculum Preparation	Nephelometer	Same
Specimen	Isolated colonies from cultures	Same
Test Organism	<i>Streptococcus</i> species other than <i>S. pneumoniae</i>	Same
Test Medium	Cation adjusted Mueller-Hinton broth with TES buffer and lysed horse blood	Same
Antibiotic	Clindamycin	Same
Incubation Time	20-24 hours	Same
Incubation Temperature	34 – 36 °C	Same
Incubation Atmosphere	Aerobic, non-CO ₂	Same
Reading Method	Manual or Automated	Same
Results	Results reported as minimum inhibitory concentration (MIC) and categorical interpretation (SIR).	Same

Differences		
Item	Device	Predicate
Technology	Fluorescence-based	Growth-based
Panel Inoculation	Automated inoculation using the AIM	RENOK Rehydrator/Inoculator
Instrument	Autoread or manual read	Manual read or MicroScan WalkAway System

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

M07-A9 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition, 2012

M100-S24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement, 2014

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

L. Test Principle:

Each plate (panel) is dosed with antimicrobial agents at appropriate dilutions. A standardized suspension is prepared from a pure growth of colonies and inoculated into the microtitre plate using the Sensititre AutoInoculator/AIM instrument. After the indicated hours of incubation, the microtitre plate is examined for growth to determine the MIC. Results can be read manually by visual reading of growth or automatically on an AutoRead using fluorescence. The Sensititre AutoRead 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-fluorogenic 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility was conducted at three sites using 17 *Streptococcus* isolates which included *S. anginosus*, *S. pyogenes* and *S. agalactiae*. Two additional isolates were

tested that included a species not indicated in the FDA drug label (*S. dysgalactiae*) and six isolates that had off-scale MICs. The sponsor was asked to remove these isolates from the reproducibility report. Because the reproducibility results were acceptable for all isolates, additional testing was not requested. The panels were inoculated using the Autoinoculator only. Panels were read both manually using the Vizion and using the AutoRead. The mode MIC value was determined and the reproducibility was calculated based on MICs falling within ± 1 dilution of the mode MIC value. The reproducibility studies for both the manual read method and the AutoRead method demonstrated best case acceptable performance of 100%.

b. *Linearity/assay reportable range:*

Not applicable.

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

The recommended quality control isolate (*S. pneumoniae* ATCC 49619) was tested 20 times at each site using the Sensititre panels with inocula prepared using the AutoInoculator. Readings were performed using both the manual read method and the AutoRead method. The QC isolate was tested using the reference method 20 times at each site using manual inoculation and manual read, with all results falling within the acceptable range. The clindamycin test results demonstrate that the system can produce QC results within the expected range. The FDA recommended quality control organism and the acceptable QC range is noted in Table 3. QC results obtained with the Sensititre panel and with the reference method are listed in Table 4.

Table 3: FDA recommended QC organism and expected range

QC organism	Expected range in $\mu\text{g/mL}$
<i>S. pneumoniae</i> ATCC 49619	0.03 – 0.12

Table 4: QC results obtained with the Sensititre panel using manual and AutoRead methods

QC organism	Expected MIC range ($\mu\text{g/mL}$)	Concentration ($\mu\text{g/mL}$)	Read method		
			Reference	Manual (Vizion)	AutoRead
<i>S. pneumoniae</i> ATCC 49619	0.03 – 0.12	≤ 0.015	0	0	0
		0.03	26	8	19
		0.06	34	51	40
		0.12	0	1	1
		0.25	0	0	0
		0.5	0	0	0
		1	0	0	0

Growth Failure Rate: All isolates tested during the clinical studies grew in both the reference panel and in the dried Sensititre panels.

Purity Check Plates were performed to detect contamination during the clinical testing at the clinical sites.

Inoculum Density Check: All organism suspensions were standardized spectrophotometrically. Turbidity meter readings were recorded each day of use and the inoculum density of the QC isolate was determined using traditional colony counting techniques. The mean inoculum densities were 4.2×10^5 , 6.5×10^5 , and 1.8×10^5 , for sites 1, 2 and 3, respectively, and were within the recommended ranges.

The quality control results are acceptable.

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:

Results obtained with the Thermo Scientific Sensititre dried MIC susceptibility panels with clindamycin were compared to results obtained using a frozen broth microdilution panel prepared according to CLSI M07-A9 guidelines. All isolates were tested using seven dilutions of clindamycin. Dilutions tested were appropriate for the interpretive breakpoints established for the drug.

Test inocula were standardized using a spectrophotometric method; Sensititre panels were inoculated using the Autoinoculator and read using the both the manual read method (Vizion) and the AutoRead method. Reference panels were inoculated as outlined in the CLSI M07-A9 document and were read manually.

The device labeling indicates that the *Haemophilus influenzae*/*Streptococcus pneumoniae* MIC panels can be manually inoculated. However, this procedural option was not utilized for testing either the clinical isolates or the challenge isolates. Therefore, the sponsor was asked to include a limitation in the device package insert stating, “*The performance of clindamycin with Streptococcus spp. was performed*

using the AIM autoinoculator. The use of an alternative inoculation system when testing clindamycin has not been evaluated.”

Seventy-five clinical isolates of *Streptococcus* were tested at each of three sites for a total of 225 *Streptococcus* isolates. The species tested included *S. agalactiae* (90 isolates), *S. pyogenes* (90 isolates) and *S. anginosus* (45 isolates). All isolates were fresh clinical isolates; no stock isolates were tested during the clinical studies.

A total of 60 challenge isolates were tested at one site. Isolates included *S. pyogenes* (25 isolates), *S. agalactiae* (25 isolates) and *S. anginosus* (10 isolates). Organism selection for the challenge isolates was based on the intended use of clindamycin for this submission. Expected results for the challenge isolates were determined using a frozen reference panel prepared using CLSI M07-A9 guidelines. Challenge isolates were tested using inocula prepared using the AutoInoculator and were read both manually and with AutoRead.

Combined results from clinical and challenge studies demonstrated an overall EA of 99.6% and an overall CA of 100% for both manual read and AutoRead. The performance evaluation summary of essential and categorical agreement results for challenge and clinical isolates (all results combined and results by species) are shown in the tables 5 - 8 below.

EA = Essential Agreement
R = Resistant Isolates
maj = major discrepancies

CA = Category Agreement
min = minor discrepancies
vmj = very major discrepancies\

Table 5: Overall performance of clinical and challenge isolates, AutoRead method

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
Clinical	225	224	99.6	176	175	99.4	225	100	42	0	0	0
Challenge	60	60	100	54	54	100	60	100	6	0	0	0
Combined	285	284	99.6	230	229	99.6	285	100	48	0	0	0

Table 6: Performance of clinical and challenge isolates by species, AutoRead method

	EA TOT	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	No. R	min	maj	vmj
<i>S. agalactiae</i>												
Clinical	90	90	100	60	60	100	90	100	32	0	0	0
Challenge	25	25	100	22	22	100	25	100	3	0	0	0
Combined	115	115	100	82	82	100	115	100	35	0	0	0

<i>S. pyogenes</i>												
Clinical	90	90	100	87	87	100	90	100	2	0	0	0
Challenge	25	25	100	25	25	100	25	100	0	0	0	0
Combined	115	115	100	112	112	100	115	100	2	0	0	0

<i>S. anginosus</i>												
Clinical	45	44	97.8	29	28	96.6	45	100	8	0	0	0
Challenge	10	10	100	7	7	100	10	100	3	0	0	0
Combined	55	54	98.2	36	35	97.2	55	100	11	0	0	0

Table 7: Overall performance of clinical and challenge isolates, manual read method

	Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
Clinical	225	224	99.6	189	189	100	225	100	42	0	0	0
Challenge	60	60	100	54	54	100	60	100	6	0	0	0
Combined	285	284	99.6	243	243	100	285	100	48	0	0	0

Table 8: Performance of clinical and challenge isolates by species, manual read method

	EA TOT	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	No. R	min	maj	vmj
<i>S. agalactiae</i>												
Clinical	90	90	100	70	70	100	90	100	32	0	0	0
Challenge	25	25	100	22	22	100	25	100	3	0	0	0
Combined	115	115	100	92	92	100	115	100	35	0	0	0
<i>S. pyogenes</i>												
Clinical	90	89	98.9	87	87	100	90	100	2	0	0	0
Challenge	25	25	100	25	25	100	25	100	0	0	0	0
Combined	115	114	99.1	112	112	100	115	100	2	0	0	0
<i>S. anginosus</i>												
Clinical	45	45	100	32	32	100	45	100	8	0	0	0
Challenge	10	10	100	7	7	100	10	100	3	0	0	0
Combined	55	55	100	39	39	100	55	100	11	0	0	0

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 9: FDA interpretive criteria for clindamycin

Organism	Susceptibility Interpretive Criteria (MIC in µg/mL)*†		
	S	I	R
<i>S. pneumoniae</i> , <i>Streptococcus</i> species (<i>S. anginosus</i> , <i>S. pyogenes</i> , <i>S. agalactiae</i>)	≤ 0.25	0.5	≥ 1

* These interpretive standards for *S. pneumoniae* and other *Streptococcus* spp. are applicable only to tests performed by broth microdilution using cation-adjusted Mueller Hinton broth with 2 to 5 % lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35 °C for 20 to 24 hours.

† S, Susceptible; I, Intermediate; R, Resistant

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.