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

A. 510(k) Number:

K183324

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Omadacycline at concentrations of 0.008 – 32 µg/mL to the Sensititre 20-24-hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System for testing *H. influenzae* and *Streptococcus* spp.

C. Measurand:

Omadacycline in the dilution range of 0.008 – 32 µg/mL.

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST), growth-based detection

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

Sensititre 20 - 24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Omadacycline in the dilution range of 0.008 - 32 µg/mL

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code:

JWY – Manual Antimicrobial Susceptibility Test System

LRG – Instrument for Auto Reader and Instrumentation of Overnight Susceptibility Systems

LTT – Panels, Test, Susceptibility, 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 20 - 24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of fastidious isolates.

This 510(k) is for Omadacycline in the dilution range of 0.008 - 32 µg/mL for testing *Streptococcus* spp. and *Haemophilus influenzae* on the Sensititre 20 - 24 hour MIC panel.

Omadacycline has been shown to be active both clinically and *in vitro* against the following organisms according to the FDA drug label:

Streptococcus pneumoniae
Haemophilus influenzae
Streptococcus anginosus group (includes *S. anginosus, S. intermedius*, and *S. constellatus*)
Streptococcus pyogenes

3. Special conditions for use statement(s):

For prescription use only

The following limitations are included in the labeling:

> *The testing of omadacycline with Streptococcus spp. was performed using the AutoReader (OptiRead) and VIZION reading methods and Haemophilus influenzae was only read by VIZION manual method. The use of an alternative*

reading method when testing omadacycline has not been evaluated.

The ability of the Sensititre system to detect resistance to Omadacycline in the following species is unknown because resistant strains were not available at the time of comparative testing: H. influenzae, S. pneumoniae, S. pyogenes, and S. anginosus. Isolates yielding omadacycline MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory for further testing.

The performance of Omadacycline with Haemophilus influenzae and Streptococcus spp. was performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Omadacycline has not been evaluated.

Omadacycline MIC values tended to be in exact agreement or at least one dilution lower when testing S. pyogenes and S. pneumoniae with both OptiRead and VIZION reading methods compared to the CLSI reference broth microdilution. MIC values MIC values tended to be in exact agreement or one dilution higher when testing S. anginosus with both OptiRead and VIZION. Omadacycline MIC values tended to be in exact agreement or at least one dilution lower when testing H. influenzae with the VIZION only.

4. Special instrument requirements:
   Sensititre AIM for device inoculation
   Sensititre VIZION or OptiRead for plate reading

I. Device Description:

Sensititre MIC Susceptibility MIC panels are multi-well microtiter plates, dosed with dried, stabilized antimicrobials. It is a miniaturized version of the classic broth dilution method and can provide both qualitative and quantitative susceptibility results. After inoculation, plates are sealed with an adhesive seal, incubated at 34 – 36 °C for 20 – 24 hours and examined for bacterial growth.

Antimicrobial susceptibility test results can be determined by reading growth using the digital viewing device (VIZION) or automatically on an autoreader (OptiRead) using fluorescence.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Sensititre *Haemophilus/Streptococcus pneumoniae* (HP) MIC Plates

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

K040846

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	**Device K183324 Sensititre *Haemophilus/Streptococcus pneumoniae* (HP) MIC Plates with Omadacycline**	**Predicate K040846 Sensititre *Haemophilus/Streptococcus pneumoniae* (HP) MIC Plates with Ertapenem**
Intended 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.	Same
Test Panel	96 well plate is dosed with selected antimicrobial agents and substrate for the fluorescent reads, then dried. The bacterial suspension in the appropriate broth is used to rehydrate the plate.	Same
Test Organism	*Haemophilus influenzae, Streptococcus pneumoniae,* and *Streptococcus* spp.	Same
Reading Methods for *Streptococcus* spp	Results can be read using the following methods: 1) Automatically with the OptiRead (fluorescent substrate technology) 2) On the VIZION (digital viewing device)	Same
Reading Methods for *H. influenzae*	Results can be read using the VIZION (digital viewing device) only	Same
Incubation	20-24 hours, 35 ± 1° C	Same
Inoculation media	CAMHBT + LHB (*Streptococcus* spp.), HTM broth (*H. influenzae*)	Same

Differences		
Item	Device	Predicate
Antimicrobial Agent	Omadacycline	Cefepime
Concentration Range	0.008 – 32 µg/mL	0.008 – 16 µg/mL

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

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

CLSI M100-S027: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh Informational Supplement

CLSI M7-A10: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition

L. Test Principle:

The Sensititre 20 - 24 hour *Haemophilus influenzae/Streptococcus pneumoniae* system includes multi-well plastic microtiter plates that contain doubled dilution of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read by the digital device, VIZION, or by use of an automated reader, OptiRead (*Streptococcus* spp. only).

The VIZION allows the panel image to be displayed on a touch screen directly from a video camera and allows the user to visually determine MIC results. The Sensititre OptiRead utilizes fluorescence technology to read the microbroth dilution plates after 20 to 24 hours incubation. 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 fluorogenic substrate. The substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The enzymatic action of the bacterial surface enzymes on the substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The substrate can be added to the inoculum broth which is dispensed into the test plate at the same time as the test organism, or, the plates can be prepared with the substrate already added to each micro-well.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   A reproducibility study was performed at four sites using a panel comprised of 8 isolates of *Streptococcus* spp.: (*S. pyogenes* (one isolate), *S. pneumoniae* (three isolates), *S. anginosus* (two isolates), and *S. agalactiae* (two isolates)) and a panel comprised of 10 strains of *H. influenzae*. Of the *Streptococcus* spp., one non-indicated species was tested. All isolates were tested in triplicate over three days with each read method (i.e., VIZION and OptiRead for *Streptococcus* spp., and VIZION only for *H. influenzae*). The Sensititre Aim inoculator was used for plate inoculation. The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. Reproducibility was greater than 95% for both read methods with *Streptococcus* spp. and VIZION with the *H. influenzae* panel and was considered to be acceptable.

   b. Linearity/assay reportable range:

   Not applicable

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

   Quality control strains recommended by the CLSI were tested with Omadacycline at four sites. The QC organisms tested were *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247. They were tested a minimum of 20 times per site and read using the VIZION and OptiRead for *S. pneumoniae* and VIZION only for *H. influenzae*. The results demonstrate that the Sensititre 20 - 24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Omadacycline produced quality control results in the recommended range >95% of the time (Table 2).

Table 2. Quality Control Results for Sensititre 20 - 24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Omadacycline with the VIZION and OptiRead Methods.

QC Organism	Omadacycline Range (µg/mL)	Concentration (µg/mL)	Reference	Sensititre	
				Read method	
				VIZION	OptiRead
S. pneumoniae ATCC 49619	0.015 – 0.12	0.008	0	0	0
		0.015	6	16	17
		0.03	76	72	71
		0.06	6	1	1
		0.12	1	0	0
		0.25	0	0	0
H. influenzae ATCC 49247	0.5 - 2	0.25	0	0	NA
		0.5	8	18	NA
		1	29	68	NA
		2	44	5	NA
		4	0	0	NA

Inoculum Density. Inoculum density checks were performed a sufficient number of times; all organism suspensions were in the acceptable range.

Purity checks. Purity checks were performed on all isolates following plate inoculation. Only results from pure cultures were evaluated.

Growth Failure: All *H. influenzae* and *Streptococcus* isolates tested showed growth in the Sensititre panels.

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 Sensititre 20 - 24 hour *Haemophilus influenzae/Streptococcus pneumoniae* MIC or Breakpoint Susceptibility System with Omadacycline were compared to results obtained with the CLSI broth microdilution reference panel. Drug dilutions were prepared using fresh Mueller Hinton broth with lysed horse blood (LHB) for *Streptococcus* spp. and Haemophilus Test Medium (HTM) broth for *H. influenzae* isolates as indicated in CLSI M07, 11th ed. Clinical testing was performed at four sites, three of which were in the U.S. A total of 352 clinical *Streptococcus* isolates were tested and read by both VIZION and OptiRead which were comprised of the following species: *S. pneumoniae* (199 isolates), *S. pyogenes* (100 isolates), and *S. anginosus* (53 isolates). In addition, a total of 393 *H. influenzae* isolates were tested of which results were read using the digital viewing device (VIZION) only. All of the clinical isolates tested were fresh isolates. During the course of the clinical trial, all Sensititre dried MIC panels were inoculated using the Sensititre Autoinoculator (AIM) and the same panel was read on both the VIZION and the OptiRead for *Streptococcus* isolates in a blinded manner. The sponsor added the following limitations to the device labeling to reflect these inoculation and read methods:

> *The performance of Omadacycline with Haemophilus influenzae and Streptococcus spp. was performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Omadacycline has not been evaluated.*
>
> *The testing of omadacycline with Streptococcus spp. was performed using the AutoReader (OptiRead) and VIZION reading methods and Haemophilus influenzae was only read by VIZION manual method. The use of an alternative reading method when testing omadacycline has not been evaluated.*

A total of 144 challenge isolates were tested at a single site. Species tested included *S. pneumoniae* (50 isolates), *S. pyogenes* (20 isolates), *S. anginosus* (24 isolates), and *H. influenzae* (50 isolates).

For *Streptococcus* spp*.,* results were evaluated for essential agreement (EA) and category agreement (CA). The susceptibility interpretive criteria (breakpoints) for Community Acquired Bacterial Pneumonia (CABP) were used to evaluate CA for *S. pneumoniae* isolates and *H. influenzae*. The breakpoints for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) were used to evaluate CA for *S. pyogenes* and *S. anginosus* group. Breakpoints for both are noted on the FDA-Recognized Susceptibility Test Interpretive Criteria Website (STIC)

(https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm).

Performance results for *Streptococcus spp.* and *H. influenzae* using the VIZION are shown in Table 3. Performance results for *Streptococcus spp.* Using the OptiRead are shown in Table 4. *H. influenzae* was only read by VIZION method.

The results from clinical and challenge testing determined with the VIZION for *H. influenzae* demonstrated a combined EA of 98% and CA of 98.9%. A total of 441 isolates were determined to have evaluable results; the EA of evaluable results was 98% (Table 3).

Clinical and challenge isolate results for the *S. pneumoniae* determined with the VIZION demonstrated a combined EA of 97.2% and CA of 99.6%. A total of 248 isolates were determined to have evaluable results; the EA of evaluable results was 97.2% (Table 3). For MIC results determined with OptiRead, the combined results from clinical and challenge testing demonstrated an EA of 97.2% and CA of 99.6%; EA of evaluable results was 97.2% (Table 4).

For *S. pyogenes,* the combined MIC results from clinical and challenge testing determined with the VIZION demonstrated EA of 99.2% and CA 97.5%; EA of evaluable results was 99.2% (Table 3). For MIC results determined with OptiRead, the combined results from clinical and challenge testing demonstrated an EA of 99.2% and CA of 100%; EA of evaluable results was 99.2% (Table 4).

S. anginosus group isolates were not speciated during the course of the study and, therefore, performance for each species was not evaluated. There were six results for both VIZION and OptiRead that were off-scale by the reference method, however, these results were deemed evaluable for essential agreement determination given that all results were at least two dilutions from the lowest dilution of the reference. The combined MIC results from clinical and challenge testing determined with the VIZION demonstrated EA of 90.9% and CA 96.1%; EA of evaluable results was 90.1% (Table 3). For MIC results determined with OptiRead, the combined results from clinical and challenge testing demonstrated an EA of 90.0% and CA of 96.1%; EA of evaluable results was 88.7% (Table 4). Only one isolate was considered resistant by the reference method. The OptiRead gave a false susceptible result with this isolate, resulting in one VMJ error. The OptiRead gave no major errors. Given that results for *S. anginosus* trended towards major errors and not very major errors, this one very major error was considered a random error and deemed acceptable.

For all organisms tested, an insufficient number of resistant isolates were encountered during the clinical evaluation. The sponsor included the following limitation in the device labeling:

> *The ability of the Sensititre system to detect resistance to Omadacycline in the following species is unknown because resistant strains were not available at the*

time of comparative testing: H. influenzae, S. pneumoniae, S. pyogenes, and S. anginosus. Isolates yielding omadacycline MIC results suggestive of a resistant interpretive category should be submitted to a reference laboratory for further testing.

Table 3. Performance of *Streptococcus* spp. and *H. influenzae* Clinical and Challenge Isolates, CABP and ABSSSI Breakpoints Read Using VIZION

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
***Streptococcus pneumoniae* CABP breakpoints (≤0.12, 0.25, ≥0.5)**													
Clinical	199	197	99.0	198	196	99.0	199	100	0	198	0	0	0
Challenge	50	45	90.0	50	45	90.0	49	98.0	0	49	1	0	0
Total	249	242	97.2	248	241	97.2	248	99.6	0	247	1	0	0
***Streptococcus pyogenes* ABSSSI breakpoints (≤0.12, 0.25, ≥0.5)**													
Clinical	100	99	99.0	100	99	99	98	98.0	1	97	2	0	0
Challenge	20	20	100	20	20	100	19	95.0	1	19	1	0	0
Total	120	119	99.2	120	119	99.2	117	97.5	2	116	3	0	0
***Streptococcus anginosus* group ABSSSI breakpoints (≤0.12, 0.25, ≥0.5)**													
Clinical	53	46	86.8	47	40	85.1	52	98.1	0	52	1	0	0
Challenge	24	24	100	24	24	100	22	91.7	1	21	2	0	0
Total	77	70	90.9	71	64	90.1	74	96.4	1	73	3	0	0
***H. influenzae* CABP breakpoints (≤2, 4, ≥8)**													
Clinical	393	389	99.0	391	387	99.0	388	98.7	2	385	5	0	0
Challenge	50	45	95.0	50	45	95.0	50	100	0	49	0	0	0
Total	443	434	98.0	441	432	98.0	438	98.9	2	434	5	0	0

EA – Essential Agreement (+/- 1 dilution)
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates

min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Table 4. Performance of *Streptococcus* spp. Clinical and Challenge Isolates, CABP and ABSSSI Breakpoints Read Using OptiRead

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
***Streptococcus pneumoniae* CABP breakpoints (≤0.12, 0.25, ≥0.5)**													
Clinical	199	197	99.0	99	99	100	199	100	0	198	0	0	0
Challenge	50	45	90.0	50	45	90.0	49	98.0	0	49	1	0	0
Total	249	242	97.2	248	241	97.2	248	99.6	0	247	1	0	0
***Streptococcus pyogenes* ABSSSI breakpoints (≤0.12, 0.25, ≥0.5)**													

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Clinical	100	99	99.0	100	99	99	98	98.0	1	97	2	0	0
Challenge	20	20	100	20	20	100	19	95.0	1	19	1	0	0
Total	120	119	99.2	120	119	99.2	117	97.5	2	116	3	0	0
***Streptococcus anginosus* group ABSSSI breakpoints (≤0.12, 0.25, ≥0.5)**													
Clinical	53	46	86.8	47	40	85.1	52	98.1	0	52	1	0	0
Challenge	24	23	95.8	24	23	95.8	22	91.7	1	21	2	0	1
Total	77	69	90.0	71	63	88.7	74	96.1	1	73	3	0	0

To address the testing of non-indicated species the following footnote was included in the precautions section of the device labeling:

> *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.*

MIC Trending

An analysis of trending was conducted using the combined clinical and challenge data for each organism group. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method irrespective of whether the device MIC values are on-scale or not. Trending results are shown in Table 5 for *H. influenzae* and for *Streptococcus* spp.. The acceptable percent difference between higher and lower dilution readings is <30%.

Table 5. Trending for All Fastidious Clinical and Challenge Isolates

Read Method	Organism	Total evaluable for trending	≥ 1 dilution lower No. (%)	Exact No (%)	≥ 1 dilution higher No (%)
VIZION	*S. pyogenes*[a]	120	60 (50)	55 (45.8)	5 (4.17)
	S. pneumoniae[b]	249	157 (63.1)	84 (33.7)	8 (3.21)
	S. anginosus[c]	74	5 (6.8)	29 (39.2)	40 (54.1)
	S. agalactiae[d]	126	85 (67.5)	36 (28.6)	5 (4.0)
	H. influenzae[e]	342	260 (76.0)	132 (38.6)	50 (14.62)
OptiRead	*S. pyogenes*[f]	120	56 (46.7)	57 (47.5)	7 (5.8)
	S. pneumoniae[g]	248	166 (66.9)	77 (31.1)	5 (2.0)
	S. anginosus[h]	74	14 (18.9)	23 (31.1)	37 (50)
	S. agalactiae[i]	126	106 (84.1)	15 (11.9)	5 (4.0)

[a] Difference between the higher and lower dilutions for *S. pyogenes* is: -45.8%
[b] Difference between the higher and lower dilutions for *S. pneumoniae* is: -59.8%
[c] Difference between the higher and lower dilutions for *S. anginosus* group is: 47.3%
[d] Difference between the higher and lower dilutions for *S. agalactiae* is: -63.5%
[e] Difference between the higher and lower dilutions for *H. influenzae* is: -61.4%
[f] Difference between the higher and lower dilutions for *S. pyogenes* is: -40.8%
[g] Difference between the higher and lower dilutions for *S. pneumoniae* is: -64.9%
[h] Difference between the higher and lower dilutions for *S. anginosus* is: 31.08%
[I] Difference between the higher and lower dilutions for *S. agalactiae* is: -80.16%

A trend toward lower MIC readings was observed for *S. pyogenes* and *S. pneumoniae* with both VIZION and OptiRead. In addition, a trend toward higher MIC readings was observed for *S. anginosus* group isolates for both VIZION and OptiRead. Furthermore, a trend toward lower MIC readings was observed for *H. influenzae* with the VIZION. The sponsor included the following footnotes to the performance table to address the trending observed for Omadacycline.

> *Omadacycline MIC values tended to be in exact agreement or at least one dilution lower when testing S. pyogenes and S. pneumoniae with both OptiRead and VIZION reading methods compared to the CLSI reference broth microdilution. MIC values MIC values tended to be in exact agreement or one dilution higher when testing S. anginosus with both OptiRead and VIZION.*
>
> *Omadacycline MIC values tended to be in exact agreement or at least one dilution lower when testing H. influenzae with the VIZION only.*

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 6. Interpretive Criteria for Omadacycline

Organism	Infection Type	FDA-Recognized Interpretive Criteria for Omadacycline, MIC (µg/mL)		
		S	I	R
H. influenzae	CABP	≤2	4	≥8
S. pyogenes	ABSSSI	≤0.12	0.25	≥0.5
S. anginosus group[1]	ABSSSI	≤0.12	0.25	≥0.5
S. pneumoniae	CABP	≤0.12	0.25	≥0.5

[1]*S. anginosus* group includes *S. anginosus, S. intermedius*, and *S. constellatus*.

N. Proposed Labeling:

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

O. Conclusion:

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