510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K202612

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

Sensititre 20-24 hour *Haemophilus influenzae /Streptococcus pneumoniae* MIC or Breakpoint, Susceptibility System with Autoread Dtest (containing erythromycin at 1 ug/mL and clindamycin at 0.5 ug/mL)

D Regulatory Information

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

II Submission/Device Overview:

A Purpose for Submission:

- To obtain clearance for the addition of the detection of positive inducible clindamycin resistance for *S. pneumoniae* using Vizion read.
- To obtain clearance for the addition of autoread of the Dtest broth microdilution test for the detection of inducible clindamycin resistance to the Sensititre 20-24 Hour *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC or breakpoint Susceptibility System for *S. pneumoniae*, *S. pyogenes* and *S. agalactiae.*
- To add a new positive Dtest QC strain for Vizion and autoread using ARIS/Autoreader/OptiRead.

B Measurand:

Erythromycin 1µg/mL and clindamycin 0.5 µg/mL

C Type of Test:

Qualitative Antimicrobial Susceptibility Test (AST) growth-based

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
The Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of *Haemophilus influenzae, Streptococcus pneumoniae* and *Streptococcus* spp.

The Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC or Breakpoint Susceptibility System with Dtest (containing erythromycin at 1ug/mL and clindamycin at 0.5 ug/mL) broth test for *Streptococcus pneumoniae* and *Streptococcus* spp- B-Hemolytic Group is an in vitro diagnostic product for clinical susceptibility testing.

The Dtest for broth microdilution is for the detection of inducible clindamycin resistance in Streptococcus spp. resistant to erythromycin (MICs $\geq$ 1 µg/mL) and either susceptible (MIC $\leq$ 0.25 µg/mL) or intermediate (MIC equal to 0.5 µg/mL) to clindamycin.

Dtest is intended for use with the following *Streptococcus* species:

Streptococcus pneumoniae
Streptococcus agalactiae
Streptococcus pyogenes

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

Limitation:
Studies for Dtest were performed using the Autoinoculator/AIM inoculation method and the Vizion and the ARIS/Autoreader/OptiRead read methods only. Use of alternative inoculation and read methods have not been evaluated.

D Special Instrument Requirements:
Sensititre ARIS/Autoreader/OptiRead for automated read
Sensititre Vizion

IV Device/System Characteristics:

A Device Description:
The Sensititre *Haemophilus influenza*/*Streptococcus pneumoniae* (HP) susceptibility panels are *in vitro* diagnostic devices for clinical susceptibility testing of *Haemophilus influenza, Streptococcus pneumoniae* and *Streptococcus* species. The panels are multi-well microtiter plates dosed with dried stabilized antimicrobial agents at appropriate concentrations. It is a miniaturized version of the classic broth dilution method and can provide both qualitative and quantitative susceptibility results.

A standardized organism suspension is prepared in cation-adjusted Mueller-Hinton broth with TES buffer and lysed horse blood; 100 µL of the organism suspension is inoculated into the antibiotic-containing well. After inoculation, plates are sealed with an adhesive seal, incubated at 34 to 36 °C for 20 to 24 hours and examined for bacterial growth. Results for the Dtest are read by observation of the image of the incubated panel using the Vizion Reader or automatically on an ARIS/Autoreader/OptiRead using detection of fluorescence.

B Principle of Operation:

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 ARIS/Autoreader/OptiRead automated reading instruments utilize fluorescence technology which detects bacterial growth by monitoring the activity of specific surface enzymes produced by the test organisms. 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 cleave 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. The substrate is included in the automated read inoculum broth.

Dtest is performed on isolates that are resistant to erythromycin (MICs ≥ 1µg/mL) and susceptible (≤ 0.25 µg/mL) or intermediate (MIC of 0.5 µg/mL) to clindamycin. The Dtest is performed in a single well containing 1.0 µg/mL of erythromycin and 0.5 µg/mL of clindamycin. Testing is performed using cation adjusted Mueller Hinton Broth with TES buffer and lysed horse blood. After incubation, results are interpreted by Vizion or automated read. Growth appears as turbidity or a deposit of cells at the bottom of the well (Vizion read) or by the production of a fluorescent signal (automated read). No growth or no fluorescence indicates the absence of inducible clindamycin resistance.

V *Substantial Equivalence Information:*

A Predicate Device Name(s):

Sensititre *Haemophilus influenza/Streptococcus pneumoniae* (HP) MIC Susceptibility Plates, Dtest

B Predicate 510(k) Number(s):

K133847

C Comparison with Predicate(s):

Table 1. Comparison with the Predicate

Device & Predicate Device(s):	**Device K202612**	**Predicate K133847**
Device Trade Name	Sensititre *Haemophilus influenza/Streptococcus pneumoniae* (HP) MIC Susceptibility Plates, Dtest	Sensititre *Haemophilus influenza/Streptococcus pneumoniae* (HP) MIC Susceptibility Plates, Dtest
General Device Characteristic Similarities		
Intended Use/Indications For Use	Sensititre *Haemophilus influenzae/Streptococcus pneumoniae* (HP) MIC Susceptibility plate is an *in vitro* diagnostic product for clinical susceptibility testing of *Haemophilus influenzae; Streptococcus pneumoniae and Streptococcus species*.	Same
Technology	Broth microdilution (MIC) susceptibility test	Same
Specimen	Isolated colonies from pure culture	Same
Inoculation Method	Automated (AutoInoculator AIM) after preparation of a standard suspension	Same
Instrument	Automated on an ARIS/Autoreader/ OptiRead using fluorescence, on the Vizion.	Same
Incubation Temperature	34-36 °C	Same
Incubation Atmosphere	Ambient air	Same
Incubation Time	20-24 hours	Same
Result	Qualitative	Same
Antimicrobial Agents	Clindamycin (0.5 µg/mL and erythromycin 1.0 µg/mL)	Same
General Device Characteristic Differences		

Indicated Species	*S. pneumoniae, S. pyogenes, S. agalactiae*	*S. pneumoniae* Dtest negative, *S. pyogenes, S. agalactiae*
Reading Method	Detection of growth or detection of fluorescence	Detection of growth

VI Standards/Guidance Documents Referenced:

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

For Clinical Study #1:
CLSI M07-A9, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard*. 2012.
CLSI M100-S23, *Performance Standards for Antimicrobial Susceptibility Testing; Twenty Third Informational Supplement*. 2013.

For Clinical Study #2
CLSI M07-A11, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard*. 2018.
CLSI M100-S30, *Performance Standards for Antimicrobial Susceptibility Testing; Twenty Third Informational Supplement*. 2020.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   A reproducibility study of Dtest was performed at three sites during two clinical studies. For Clinical Study #1 a total of 23 *Streptococcus* species were evaluated including *S. pneumoniae* (5 isolates, 1 Dtest positive, 4 Dtest negative), *S. pyogenes* (8 isolates, 2 Dtest positive, 6 Dtest negative) and *S. agalactiae* (10 isolates, 4 Dtest positive, 6 Dtest negative). Isolates were tested once at each of the three sites for a total of 69 data points.

   For Clinical Study #2 a total of 11 *Streptococcus* species were evaluated including *S. pneumoniae* (4 isolates, 1 Dtest positive, 3 Dtest negative), *S. pyogenes* (4 isolates, 4 Dtest negative) and *S. agalactiae* (3 isolates, 2 Dtest positive and 1 Dtest negative). Isolates were tested in triplicate on each of three days at each site for a total of 297 data points. Plates were inoculated with the AutoInoculator/AIM after preparation of a standard suspension. All results were interpreted using VIZION and ARIS/Autoreader/OptiRead. Reproducibility was greater than 95% for both read methods for both clinical trials. The reproducibility is acceptable.

2. Linearity:
   Not applicable

3. Analytical Specificity/Interference:
   Not applicable

4. Assay Reportable Range:
   Not applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
   Quality Control strains recommended by CLSI were tested with Dtest at three sites. The QC organisms tested were *S. pneumoniae* ATCC 49610 as a negative control and *S. aureus* ATCC BAA-977 as a positive control. The *S. aureus* QC strain gives uninterpretable results for Dtest with ARIS/Autoreader/OptiRead. This appears to be due to the inability to obtain accurate reading and interpretation possibly due to interaction with lysed horse blood in the test media. This QC strain can be used only for Vizion read.

   In both Clinical study #1 and Clinical study #2, a strain of *S. agalactiae* (SGB20), which provides a positive Dtest result with the ARIS/Autoreader/OptiRead method was included in the QC testing. As the *S. agalactiae* SGB20 strain is not recommended by CLSI, validation was required. Validation was performed at five clinical sites, using 2 lots of Sensititre panels, with testing occurring over 20 days at each site (one test per day) for a total of 120 data points. Results were interpreted using Vizion and ARIS/Autoreader/OptiRead. All tests provided the expected results with both Vizion and the ARIS/Autoreader/OptiRead method using the Sensititre dried panels and with the reference method. The strain will be made available to users in disposable inoculating loops that contain the stabilized, preserved and viable organism.

   The sponsor included the following information in the QC table indicating the appropriate positive QC strain for each read method:

   Dtest
   S. pneumoniae ATCC 49619 — Negative (no growth)
   S. aureus ATCC BAA-977 — Positive (growth) Vizion only
   S. agalactiae SGB20 — Positive (growth) Vizion/AutoRead

Table 2. Quality Control Results for Dtest with the Reference, VIZION and ARIS/Autoreader/OptiRead Methods.

QC Organism	Expected Result	Clinical Trial	Reference		VIZION		ARIS/Autoreader /OptiRead	
			POS	NEG	POS	NEG	POS	NEG
S. pneumoniae ATCC 49619	Neg	1	0	20	0	20	0	20
		2	0	20	0	20	0	20
S. aureus ATCC BAA-977	Pos	1	20	0	20	0	NA*	NA
		2	20	0	20	0	NA	NA
S. agalactiae SGB20	Pos	1	20	0	20	0	20	0
		2	20	0	20	0	20	0

*Not Applicable, results not interpretable with ARIS/Autoreader/OptiRead

Inoculum Density. Inoculum density checks were performed a sufficient number of times; overall inoculum density results were acceptable.

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

Growth Failure: all isolates tested showed growth in the Sensititre panels

6. Detection Limit:
   Not applicable

7. Assay Cut-Off:
   Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
   Two clinical studies were used to collect data on the performance of Dtest on the Sensititre *Haemophilus/Streptococcus Pneumoniae* (HP) Susceptibility Plate. For both clinical studies, testing was performed at three sites, one site in each study was internal.

   Results obtained with Sensititre *Haemophilus*/*Streptococcus Pneumoniae* (HP) Susceptibility Plate Dtest were compared to results obtained with results obtained using the CLSI broth microdilution reference method, read manually (visually) in accordance with CLSI recommendations. Testing for both the reference and Sensititre test was performed in a single well containing a combination of erythromycin (1µg/mL) and clindamycin (0.5 µg/mL). All Sensititre tests were inoculated using the Sensititre AutoInoculator (AIM) and read on both the VIZION and ARIS/Autoreader/OptiRead. The sponsor added the following limitations to the device labeling to reflect the procedure used for inoculation of panels in the comparative study:

   > *Studies for Dtest were performed using the Autoinoculator/AIM inoculation method and the Vizion and the ARIS/Autoreader/OptiRead read methods only. Use of alternative inoculation and read methods have not been evaluated.*

   Because this is a qualitative test, results were evaluated for category agreement and for number and percent of major and very major errors.

   ***S. pneumoniae* Dtest Positive with Vizion**. Results obtained from Clinical Study #2 were analyzed to support removal of the following limitation:

   > *The ability of the Sensititre system to detect Dtest positive S. pneumoniae isolates is unknown because Dtest positive strains were not tested at the time of comparative testing. Any S. pneumoniae isolate determined to be Dtest positive with the Sensititre system should be subjected to additional testing or submitted to a reference laboratory if necessary*.

   A total of 178 *S. pneumoniae* isolates were evaluated using Vizion read and included: 26 Dtest positive isolates (17 clinical and 9 challenge) and 152 Dtest negative isolates (118 clinical and 34 challenge). The CA for *S. pneumoniae* Dtest with Vizion read was 100% (Table 3). Results obtained with *S. pneumoniae* using Vizion were acceptable; the results

support removal of the limitation allowing reading and reporting results of Dtest positive *S. pneumoniae* isolates.

Table 3. Dtest Vizion Read with *S. pneumoniae* (Data from Clinical Study #2)

Isolates	No. Tested	CA	%CA	POS[a]	NEG[b]	maj[c]	vmj[d]
S. pneumoniae							
Clinical	135	135	100	17	118	0	0
Challenge	43	43	100	9	34	0	0
Total	178	178	100	26	152	0	0

[a] No. Inducible Clindamycin Resistance Positive by the reference method (Resistant)
[b] No. Inducible Clindamycin Resistance Negative by the reference method (Susceptible)
[c] Major errors
[d] Very major errors

Dtest with ARIS/Autoreader/OptiRead. Testing was performed to support removal of the following limitation which was previously imposed due to the lack of a suitable quality control isolate to serve as a positive control for ARIS/Autoreader/OptiRead:

> *Dtest results should be interpreted using manual read only. The ability of the Sensititre system to detect a positive Dtest by autoread cannot be confirmed due to the lack of a Dtest positive quality control isolate for autoread.*

In the current submission the sponsor validated a new quality control strain (*S. agalactiae* SGB20) for ARIS/Autoreader/OptiRead (see above); use of this newly validated QC strain allows reading and reporting of Dtest results for all species interpreted using ARIS/Autoreader/OptiRead.

***S. pneumoniae* and *S. agalactiae* Dtest with ARIS/Autoreader/OptiRead.** A total of 178 *S. pneumoniae* isolates were evaluated in Clinical Study #2 with ARIS/Autoreader/OptiRead including 26 Dtest positive isolates (17 clinical and 9 challenge) and 152 Dtest negative isolates (118 clinical and 34 challenge). A total of 93 *S. agalactiae* isolates were evaluated including 42 Dtest positive isolates (39 clinical and 3 challenge) and 51 Dtest negative isolates (34 clinical and 17 challenge). The CA for *S. pneumoniae* and *S. agalactiae* Dtest with ARIS/OptiRead was 100% (Table 4).

Table 4. *S. pneumoniae* and *S. agalactiae* Dtest with ARIS/OptiRead (Data from Clinical Study 2)

Isolates	No. Tested	CA	%CA	POS[a]	NEG[b]	maj	vmj
S. pneumoniae							
Clinical	135	135	100	17	118	0	0
Challenge	43	43	100	9	34	0	0
Total	178	178	100	26	152	0	0
S. agalacatiae							
Clinical	73	73	100	39	34	0	0
Challenge	20	20	100	3	17	0	0
Total	93	93	100	42	51	0	0

[a] No. Inducible Clindamycin Resistance Positive by the reference method (Resistant)
[b] No. Inducible Clindamycin Resistance Negative by the reference method (Susceptible)

***S. pyogenes* with ARIS/Autoreader/OptiRead.** Combined results from Clinical Studies #1 and #2 were analyzed to support testing of *S. pyogenes* with ARIS/OptiRead. A total of 93 *S. pyogenes* isolates were evaluated including 37 Dtest positive isolates (27 clinical and 10 challenge) and 185 Dtest negative isolates (100 clinical and 85 challenge). There was one false positive Dtest result resulting in a major error (0.5%). The CA for *S. pyogenes* Dtest with ARIS/OptiRead was 99.6% (Table 5).

Table 5. *S. pyogenes* Dtest with ARIS/Autoreader/OptiRead (Data from Clinical Studies 1 and 2)

Study	Isolates	No. Tested	CA	%CA	POS[a]	NEG[b]	maj	vmj
S. pyogenes								
Clinical Study 1	Clinical	90	89	98.9	9	81	1	0
	Challenge	37	37	100	18	19	0	0
	Total	127	126	99.2	27	100	1	0
Clinical Study 2	Clinical	75	75	100	9	66	0	0
	Challenge	20	20	100	1	19	0	0
	Total	95	95	100	10	85	0	0
Total Studies 1/2	Total	222	221	99.6	37	185	1	1

[a] No. Inducible Clindamycin Resistance Positive by the reference method (Resistant)
[b] No. Inducible Clindamycin Resistance Negative by the reference method (Susceptible)

The results obtained for *S. pneumoniae, S. agalactiae* and *S. pyogenes* obtained using ARIS/Autoreader/OptiRead support removal of the limitation restricting interpretation of Dtest to only Vizion read.

Based on the results obtained in this submission related to reporting results for Dtest positive isolates of *S. pneumoniae* and results obtained for ARIS/Autoreader/OptiRead with *S. pneumoniae, S. agalactiae* and *S. pyogenes*, the sponsor modified the footnote to the interpretation table in the device labeling to read:

For S. pneumoniae, S. pyogenes and S. agalactiae resistant to Erythromycin (MIC ≥ 1 µg/mL) and susceptible (MIC ≤ 0.25 µg/mL) or intermediate (MIC 0.5 µg/mL) to Clindamycin, growth in the Dtest well indicates inducible Clindamycin resistance. For S. pneumoniae, S. pyogenes and S. agalactiae, no growth in the Dtest well indicates no inducible Clindamycin resistance.

2. Matrix Comparison:
   Not applicable

C Clinical Studies:

1. Clinical Sensitivity:
   Not applicable

2. Clinical Specificity:
   Not applicable

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

D Clinical Cut-Off:
Not applicable

E Expected Values/Reference Range:

Table 6. Expected Results for Dtest

Result	Interpretation
Growth in Dtest well	Positive for inducible clindamycin resistance
No growth in Dtest well	Negative for inducible clindamycin resistance

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.