

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

A. 510(k) Number: k032194

B. Analyte: Chlamydia trachomatis and Neisseria gonorrhoeae rRNA

C. Type of Test: Automation for Aptima Combo 2 Assay

D. Applicant: Gen-Probe, Inc.

E. Proprietary and Established Names: Tigris DTS™ Gen-Probe® Aptima® Combo 2 Assay

F. Regulatory Information:

1. Regulation section: 21 CFR Part 866.3390 and 866.3120, Chlamydia Serological Reagents and Neisseria spp. Direct Serological Test Reagents
2. Classification: Class II
3. Product Code: LSL and MKZ
4. Panel: 83

G. Intended Use: The APTIMA Combo 2 Assay is a target amplification nucleic acid probe test that utilizes target capture for the *in vitro* qualitative detection and differentiation of ribosomal RNA (rRNA) from *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* in endocervical and male urethral swab specimens, and in female and male urine specimens. The assay may be used to test specimens from symptomatic and asymptomatic individuals to aid in the diagnosis of gonococcal and/or chlamydial urogenital disease using the TIGRIS DTS Automated Analyzer or semi-automated instrumentation as specified.

1. Indication(s) for use: The assay may be used to test specimens from symptomatic and asymptomatic individuals to aid in the diagnosis of gonococcal and/or chlamydial urogenital disease using the TIGRIS DTS Automated Analyzer or semi-automated instrumentation as specified.
2. Special condition for use statement(s): The Tigris DTS can only be used with specimens collected in the Aptima Unisex Swab Specimen Collection kit and the Aptima Urine Specimen Collection kit. PACE Specimen Collection Kits cannot be adapted for use on the Tigris DTS.

3. Special instrument Requirements: The Tigris DTS instrument is an automated analyzer that has been validated for use with the modified Aptima Combo 2 Assay reagents and procedure.

H. Device Description:

The reagents for the Tigris DTS APTIMA® Combo 2 assay are unchanged from the semi-manual version. The Tigris instrument platform was developed to fully automate all steps necessary to perform the APTIMA® Combo 2 assay from sample processing through amplification, detection and data reduction. Volumes of reagents are modified for use on the automated instrument, the TIGRIS DTS System.

The two main components of the TIGRIS DTS System are the analyzer and the computer workstation. The computer workstation directs the analyzer modules to perform each assay step. The analyzer houses all of the fluids, reagents, consumables, and mechanical parts that perform the assay.

These mechanical parts include a fluid delivery module (syringes, pumps, and valves), holding areas for reagents and waste products, a sample bay (for loading sample racks, pipette tips and TCR reagent), pipettors for reagents and samples, syringes for dispensing reagents and specimens, a magnetic wash station, various mixers, four incubators, and a luminometer. One sample carousel can hold up to 9 racks and each rack can hold 20 specimen tubes. An internal vacuum system controls aspiration of liquid from the magnetic wash station. Barcode scanners (one in the lower bay, one in the sample bay, one in the assay reagent bay, and others) are used for reagent and specimen tracking. System software monitors system status, reagent and supply inventories, worklists, test results, and maintenance.

I. Substantial Equivalence Information:

1. Predicate device name(s): Gen-Probe Aptima® Combo 2 Assay
2. Predicate K number(s): k003395
3. Comparison with predicate:

| Similarities | | |
|------------------------------------|--|--|
| Item | Device | Predicate |
| Intended Use | See above | Same |
| Reagent stability | Adapted for Tigris platform | See Package Insert |
| Result output | Software mediated | Software mediated |
| Analytical Sensitivity (per assay) | <0.1 IFU C. trachomatis 15 CFU N. gonorrhoeae | <0.1 CFU C. trachomatis 15 CFU N. gonorrhoeae |
| Analytical specificity | N. elongata – increased signal | N. elongata – increased signal |
| Differences | | |
| Item | Device | Predicate |
| Indications | Automated | Semi-automated |

| | | |
|-----------------|---|---|
| | All Aptima Collection tubes | All Aptima Collection tubes and Pace swab specimen tubes using adapters |
| Reagents | Reagent volume adapted for 250 tests | 100 test volumes |
| System Controls | Instrument sensors and software-mediated alerts | Operator checks during assay procedure |
| Precision | Up to 6.9% CV (intra-run) for low level CT* | Up to 16% (inter-site) for mid-level CT* |
| Carryover | 0-1.99% for 3 instruments (7/345, 0/347, 5/398) | Not known |

* Findings are not comparable because of different levels and numbers tested

J. Standard/Guidance Document Referenced (if applicable): NA

K. Test Principle: The Tigris allows full automation of the Aptima Combo 2 procedure. Specimen tubes and controls are loaded onto the instrument, along with necessary reagents and other supplies (pipet tips, MTUs, etc.). Test results are handled by software that generates printed worklists.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:* Agreement of Tigris results with expected results for spiked specimens was reduced compared to manual testing (85% vs. 100% for low level *C. trachomatis* – 0.25 IFU/mL or 0.1 IFU/assay). All other levels of *C. trachomatis* and *N. gonorrhoeae* were 100% reproducible in all specimen pools.

CT/GC Clinical Panel Agreement Study: Agreement with Expected CT and GC Results

| Panel Member CT/GC | Panel Member Concentration ¹ | | Replicates | CT | | GC | |
|-----------------------|---|-----------|------------|-------------------|-----------------|-------------------|----------------|
| | CT IFU/mL | GC CFU/mL | | TIGRIS % Agrmt | DTS % Agrmt | TIGRIS % Agrmt | DTS % Agrmt |
| Low/Low | 2.5 | 125 | 20 | 100 | 100 | 100 | 100 |
| Low/High | 2.5 | 125,000 | 20 | 100 | 95 ³ | 100 | 100 |
| High/Low | 2,500 | 125 | 20 | 100 | 100 | 100 | 100 |
| High/High | 2,500 | 125,000 | 20 | 100 | 100 | 100 | 100 |
| Very Low/Neg | 0.25 ² | 0 | 20 | 85 ⁴ | 100 | 100 | 100 |
| Low/Neg | 2.5 | 0 | 20 | 100 | 100 | 100 | 100 |
| Medium/Neg | 25 | 0 | 20 | 100 | 100 | 100 | 100 |
| High/Neg | 2,500 | 0 | 20 | 100 | 100 | 100 | 100 |
| Neg/Very Low | 0 | 12.5 | 20 | 100 | 100 | 100 | 100 |
| Neg/Low | 0 | 125 | 20 | 100 | 100 | 100 | 100 |
| Neg/Medium | 0 | 1,250 | 19 | 100 | 100 | 100 | 100 |
| Neg/High | 0 | 125,000 | 20 | 100 | 100 | 100 | 100 |

| | | | | | | | |
|---------|---|---|----|-----|-----|-----|-----|
| Neg/Neg | 0 | 0 | 20 | 100 | 100 | 100 | 100 |
|---------|---|---|----|-----|-----|-----|-----|

Overall Percent Agreement between TIGRIS and DTS (95% C.I.): 99.3% (98.3% - 99.8%)

IFU – Inclusion Forming Units, CFU – Colony Forming Units, TIGRIS %Agrmt = Agreement between TIGRIS with expected results
DTS %Agrmt = Agreement between DTS with expected results

¹A collection tube contains approximately 2.9 mL of transport medium for swab specimens and 4.0 mL of transport medium/urine mixture for urine specimens.

²The CT concentration in this CT/GC clinical panel member is one log below the APTIMA Combo 2 Assay analytical sensitivity claim of 1 IFU/assay (7.25 IFU/swab, 5 IFU/mL urine).

³One of 5 female urine panel replicates was CT- on the DTS System.

⁴Three of 5 female urine panel replicates were CT- on the TIGRIS System.

- b. Linearity/assay reportable range: NA*
RLU levels cannot be compared because the kinetic algorithm moderates interpretation
- c. Traceability (controls, calibrators, or method):* Controls are prepared in-house by the manufacturer and are not traceable to a standard or independent measure.
- d. Detection limit:*
<0.1 IFU *C. trachomatis*
15 CFU *N. gonorrhoeae*
- e. Analytical specificity:*
N. elongata – increased signal in a clean system
- f. Assay cut-off:*
The kinetic profiles were modified with the Tigris application. Although the cutoffs measured in RLU is the same, the computation of the kinetic profiles was changed (specifications for parameters A, B, C, and D and for Zone A1, A2, A4, A5, B3, C1, C2, C3 and C4)
- g. Carry-over testing performed:*

Results

| | Negative | Equivocal | Positive | Total |
|--------------|----------|-----------|----------|-------|
| Instrument 1 | 345 | 3 | 4 | 352 |
| Instrument 2 | 347 | 0 | 0 | 347 |
| Instrument 3 | 393 | 2 | 3 | 398 |
| | | | | 1097 |

2. Comparison studies:

- a. Method comparison with predicate device:*

Aptima Combo 2 testing was done with the Tigris and manual DTS on swab and urine specimens from symptomatic and asymptomatic males and females. *C. trachomatis* agreement for asymptomatic females and other groups was reduced or not statistically interpretable (lower 95% CI were <90%).

b. *Matrix comparison*: NA

3. Clinical studies: NA; the sponsor performed an evaluation of agreement between the Tigris and manual DTS on the same specimen. As a result clinical sensitivity and specificity of the Tigris could not be established.

a. *Clinical sensitivity*: NA

b. *Clinical specificity*: NA

- c. *Other clinical supportive data (when a and b are not applicable)*:
The Aptima Combo 2 assay was previously shown to have predictable performance with urine and urogenital swab specimens from males and females, both symptomatic and asymptomatic for the detection of *C. trachomatis* and *N. gonorrhoeae*. Parallel testing of these specimen types was done with the semi-manual and the fully automated Tigris system. Agreement between the two methods is shown in the attached tables. Females, especially asymptomatic females, are at highest risks for adverse consequences of a false positive or negative assay test results, and this group had the lowest agreement for both swab and urine specimen types when *Chlamydia trachomatis* was detected by the semi-manual method.

For CT swab testing, for both asymptomatic males and asymptomatic females, point estimates for positive agreement is <95% and lower confidence boundaries are both <75%. GC agreement had reduced positivity (<95%) with asymptomatic males and also symptomatic females. Even when all groups are combined, for swabs tested by Tigris for both males and females, agreement is 90% (83.2 – 94.7%, 95% CI) with AC2CT+/GC- done semi-manually; agreement for urines is 92.6% (85.9 – 96.7% CI) overall for CT+/GC-.

Qualitative Agreement findings for clinical specimens (tested at Gen-Probe)

Clinical Specimen Agreement Study: Swab Specimen Results ¹

| TIGRIS System | DTS System | | | | Total |
|---------------|----------------|-----------------|----------------|----------------|-------|
| | CT+/GC+ | CT+/GC- | CT-/GC+ | CT-/GC- | |
| CT+/GC+ | 30 | 0 | 0 | 0 | 30 |
| CT+/GC- | 0 | 108 | 0 | 2 ⁵ | 110 |
| CT-/GC+ | 1 ² | 0 | 67 | 0 | 68 |
| CT-/GC- | 0 | 12 ³ | 2 ⁴ | 796 | 810 |

| | | | | | |
|---|-------|-------|-------|-------|------|
| Total | 31 | 120 | 69 | 798 | 1018 |
| Percent | 96.8% | 90.0% | 97.1% | 99.7% | n/a |
| Overall Percent Agreement (95% C.I.): 98.3% (97.3% - 99.0%) | | | | | |

+ denotes Positive, - denotes Negative, n/a = Not Applicable

Clinical Specimen Agreement Study: Urine Specimen Results

| TIGRIS System | DTS System | | | | Total |
|---|------------|----------------|----------------|----------------|-------|
| | CT+/GC+ | CT+/GC- | CT-/GC+ | CT-/GC- | |
| CT+/GC+ | 32 | 0 | 0 | 0 | 32 |
| CT+/GC- | 0 | 100 | 0 | 1 ³ | 101 |
| CT-/GC+ | 0 | 0 | 52 | 0 | 52 |
| CT-/GC- | 0 | 8 ¹ | 1 ² | 776 | 785 |
| Total | 32 | 108 | 53 | 777 | 970 |
| Percent | 100% | 92.6% | 98.1% | 99.9% | n/a |
| Overall Percent Agreement (95% C.I.): 99.2% (98.1% - 99.5%) | | | | | |

+ denotes Positive, - denotes Negative, n/a = Not Applicable

Clinical Specimen Agreement Study: CT Results

| Gender | Specimen | Symptom | N | DTS+ TIGRIS+ n | DTS+ TIGRIS- ¹ n | DTS- TIGRIS+ n | DTS- TIGRIS- n | Positive Agreement (95% C.I.) | Negative Agreement (95% C.I.) |
|--------|----------|--------------|------|-------------------|--------------------------------|-------------------|-------------------|----------------------------------|----------------------------------|
| All | Swab | Symptomatic | 425 | 84 | 3 ² | 0 | 338 | 96.6 (90.3-99.3) | 100 (98.9-100) |
| | | Asymptomatic | 596 | 54 | 10 ³ | 2 ⁶ | 530 | 84.4 (73.1-92.2) | 99.6 (98.6-100) |
| | | All | 1021 | 138 | 13 | 2 | 868 | 91.4 (85.7-95.3) | 99.8 (99.2-100) |
| | Urine | Symptomatic | 407 | 80 | 4 ⁴ | 0 | 323 | 95.2 (88.3-98.7) | 100 (98.9-100) |
| | | Asymptomatic | 563 | 52 | 4 ⁵ | 1 ⁷ | 506 | 92.9 (82.7-98.0) | 99.8 (98.9-100) |
| | | All | 970 | 132 | 8 | 1 | 829 | 94.3 (89.1-97.5) | 99.9 (99.3-100) |

Clinical Specimen Agreement Study: GC Results ¹

| Gender | Specimen | Symptom | N | DTS+ TIGRIS+ n | DTS+ TIGRIS- n | DTS- TIGRIS+ n | DTS- TIGRIS- n | Positive Agreement (95% C.I.) | Negative Agreement (95% C.I.) |
|---------------------|----------|--------------|------|-------------------|-------------------|-------------------|-------------------|----------------------------------|----------------------------------|
| All | Swab | Symptomatic | 423 | 80 | 1 ² | 0 | 342 | 98.8 (93.3-100) | 100 (98.9-100) |
| | | Asymptomatic | 595 | 18 | 1 ³ | 0 | 576 | 94.7 (74.0-99.9) | 100 (99.4-100) |
| | | All | 1018 | 98 | 2 | 0 | 918 | 98.0 (93.0-99.8) | 100 (99.6-100) |
| | Urine | Symptomatic | 407 | 72 | 1 ⁴ | 0 | 334 | 98.6 (92.6-100) | 100 (98.9-100) |
| | | Asymptomatic | 563 | 12 | 0 | 0 | 551 | 100 (73.5-100) | 100 (99.3-100) |
| | | All | 970 | 84 | 1 | 0 | 885 | 98.8 (93.6-100) | 100 (99.6-100) |
| Female ⁵ | Swab | All | 567 | 26 | 1 | 0 | 540 | 96.3 (81.0-99.9) | 100 (99.3- 100) |
| | Urine | All | 562 | 20 | 1 | 0 | 541 | 95.2 (76.2-99.9) | 100 (99.3- 100) |

| | | | | | | | | | |
|-------------------|-------|-----|-----|----|---|---|-----|------------------|-----------------|
| Male ⁵ | Swab | All | 451 | 72 | 1 | 0 | 378 | 98.6 (92.6- 100) | 100 (99.0- 100) |
| | Urine | All | 408 | 64 | 0 | 0 | 344 | 100 (94.4- 100) | 100 (98.9- 100) |

+ denotes Positive, - denotes Negative, C.I. = Confidence Interval

FDA requested additional evidence to support the comparability of the two methods. The company reported additional data from comparison of the 2 methods at an independent laboratory evaluating the automated system. In that report, disagreement was not seen for a large sampling of specimens, presumably representing the targeted population (asymptomatic females).

Additionally, a contrived panel of simulated specimens was parallel tested on the 2 systems. Agreement was shown for most levels tested, except for the female urine pool containing very low numbers of *Chlamydia trachomatis* IFUs.

Carryover studies showed that low levels of contamination could be expected (up to 2% on one of three instruments evaluated).

Warnings are included in the package insert to advise laboratories.

4. Clinical cut-off: Analytically, there was no difference in CT/GC results using the new kinetic profiles (Tigris-specific) for 5 different instruments, different temperatures (13, 15, 18-22, 25, and 27°), relative humidity of 20-80%, 2 different reagent kit lots, when AutoDetect volumes were varied, or when injection rates were varied). rRNA solutions in a clean system were used for this verification. FDA believes that these solutions may not be representative of actual testing conditions with specimen material and evaluated the differences in RLU levels for different specimen types from the parallel testing done with clinical specimens and spiked pooled specimen material.
5. Expected values/Reference range: The presence of *C. trachomatis* or *N. gonorrhoeae* in any amount is considered indicative of urogenital infection.

M. Instrument Name: Tigris DTS Automated Analyzer

N. System Descriptions:

1. Modes of Operation: Batch, closed tube
2. Software: Release version will be 1.05; FDA reviewed submitted materials for 1.04 that will be updated prior to release. The system uses Windows NT (Service Pack 6). The analyzer relies on the computer workstation for instruction, communicating system status, and results through a standard serial interface, and provides a link to the LIS.

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes or No

3. Sample Identification: Barcode and MTU/rack position

Sample tube barcodes may use any of the formats specified below. Tigris must be configured to read Code 39 and Codabar formatted barcodes. The analyzer is always enabled to read Code 128 (ISBT 128) and Code 12 of 5 (I 2 of 5) formatted barcodes. All barcodes must have 2-20 characters (with no commas) and have a feature size from 6.5 mil (0.16 mm) to 10 mil (0.245 mm).

| Type | Enable Options | Checksum Options |
|---------------------|---|--|
| Code 39 | Enabled through TIGRIS DTS checksum. | Use checksum, send System software. |
| Code 128 (ISBT 128) | Always enabled | None |
| Code I 2 of 5 | Always enabled. | No checksum allowed. |
| Codabar | Enabled through TIGRIS DTS System software. | Send checksum, send start/stop characters. |

4. Specimen Sampling and Handling: Specimens are collected (either a swab or a urine specimen) and transferred to the Aptima Specimen Collection device (swab or urine transport tubes containing transport/stabilizing medium). These tubes are placed into racks containing 20 tubes each. The tubes must be visually checked for adequate volume and precipitates.
5. Assay Types: Aptima Combo 2
6. Reaction Types: kinetic fluorescent (luminometer)
7. Calibration: SysCheck reagent for luminometer; Assay RNA controls
8. Quality Control: Assay controls are RNA preparations that would not monitor factors associated with matrix in the test system; users must prepare controls from ATCC preparations, culture growth, or use previously positive specimen material.

O. Conclusion:

The Tigris DTS test system appears to produce results similar to results obtained with the Aptima Combo 2 Assay performed as previously cleared (semi-manual). Labeling precautions and warnings are incorporated to advise users of potential errors that may occur and when software will not alert users of potential problems.