

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE**

A. 510(k) Number: K060652

B. Purpose for Submission: Modification of the Tigris DTS APTIMA® Combo 2 assay to include vaginal swab specimens and PreservCyt specimens. Originally, the Aptima Combo 2 Assay received FDA clearance on May 21, 2001 (K032554) for testing endocervical and urethral swab, and urine specimens. The Tigris DTS System was indicated for use with the Aptima Combo 2 Assay (endocervical and urethral swabs, and urine specimens from symptomatic and asymptomatic males and females) with k032194. Subsequently, vaginal swab specimens (patient- and clinician-collected) and endocervical samples collected in PreservCyt Solution processed with the Cytoc ThinPrep 2000 System were indicated (k032554 and k043224) for testing with the Aptima Combo 2 Assay.

The current submission is for additionally testing specimens collected and processed with the Cytoc ThinPrep 2000 System and vaginal swab specimens (self-collected and clinician-collected) on the Tigris DTS system for Aptima Combo 2 assay testing.

C. Measurand: *Chlamydia trachomatis* and *Neisseria gonorrhoeae* RNA

D. Type of Test: Nucleic acid amplification, hybridization protection detection

E. Applicant: Gen-Probe, Inc.

F. Proprietary and Established Names: Aptima Combo 2 Assay with Tigris DTS Automated Instrument; DNA-reagents, Neisseria

G. 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, Microbiology Devices

H. Intended Use:

1. Intended use(s):

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 clinician collected endocervical, vaginal and male urethral swab specimens, patient-collected vaginal swab specimens, female and male urine specimens and gynecological specimens collected in the PreservCyt Solution and processed with the Cytoc ThinPrep 2000 System.

2. 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.

- Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The vaginal swab specimen collection kit is not for home use.
- Gynecological specimens collected in the PreservCyt Solution and processed with the Cytoc ThinPrep 2000 System have only been reviewed and cleared for use with the APTIMA Combo 2 Assay in the United States by the Food and Drug Administration (FDA).

3. Special conditions 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.

4. Special instrument requirements: TIGRIS®DTS®™Automated Analyzer

I. Device Description:

The reagents for the TIGRIS DTS APTIMA Combo 2 Assay are unchanged from the initial submission (K032194). No new QC test methods were developed and/or validated for any material or reagents since the QC test methods have been developed and/or validated for the AC2 Assay on DTS Systems (K003395). The reagents for the Tigris DTS APTIMA® Combo 2 assay are unchanged from the semi-manual version, except for the volume provided. The Tigris instrument platform fully automates all steps necessary to perform the APTIMA® Combo 2 assay from sample processing through amplification, detection and data reduction.

J. Substantial Equivalence Information:

1. Predicate device name(s):

AC2 Assay on DTS System (K003395)

TIGRIS®DTS®™Automated Analyzer (k032194)

AC2 Assay on DTS System, for self-collection of vaginal swab specimens (k032554)

AC2 Assay on DTS System, for ThinPrep 2000 processed PreservCyt endocervical specimens (k043224)

2. Predicate 510(k) number(s): see above
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Tigris hardware	Same	Same
Aptima Combo 2 assay reagents	Same	Same
Indications	Males and females; symptomatic and asymptomatic	Same

Differences		
Item	Device	Predicate
Tigris software	Version 3.3.13	Version 1.04.04
ADM Sample scrip	Aspirate and dispense several times	Single aspirate and dispense
Vaginal swabs in STM	Automated (Tigris)	Semi-automated
ThinPrep 2000 processed PreservCyt endocervical samples	Automated (Tigris)	Semi-automated
Specimen types	Endocervical and urethral swabs, urine	Additionally vaginal swabs, and ThinPrep processed cervical samples

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

L. 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Agreement of Tigris results with expected results (and compared to agreement of DTS with expected results) from testing replicate samples prepared from pools to create 13 stock vaginal samples and 13 stock PreservCyt samples (prepared from one master pool). Each stock was spiked with varying amounts of CT and GC RNA and 10 replicates of each stock tested (with the exception of the non-spiked pool that had 12 replicates) on one Tigris instrument and also semi-manually. All 132 samples for each specimen type master pool tested on the Tigris agreed with expected results, while one very low CT (0.5 fg) was equivocal and another negative with the semi-manual (DTS) method. These data

verify that 0.5 – 5000fg CT RNA and 25-250,000 GC-RNA produce consistent positive results with the AC2 assay run on the Tigris instrument. Between-day and between-run variances were not factored in the study design. These data are more appropriately precision-type data rather than clinical agreement as represented in the package insert. Note: in a previous Tigris study, pools were unique fore each sample type and level and whole organisms were spiked.

<u>Panel Member</u>	<u>Spiking Concentration (per Reaction)</u>
1	10 spiked tubes: CT 5 fg/assay – GC 250 fg/assay
2	10 spiked tubes: CT 5 fg/assay – GC 250,000 fg/assay
3	10 spiked tubes: CT 5000 fg/assay – GC 250 fg/assay
4	10 spiked tubes: CT 5000 fg/assay – GC 250,000 fg/assay
5	10 spiked tubes: CT 0.5 fg/assay – GC 0 fg/assay
6	10 spiked tubes: CT 5 fg/assay – GC 0 fg/assay
7	10 spiked tubes: CT 50 fg/assay – GC 0 fg/assay
8	10 spiked tubes: CT 5000 fg/assay – GC 0 fg/assay
9	10 spiked tubes: CT 0 fg/assay – GC 25 fg/assay
10	10 spiked tubes: CT 0 fg/assay – GC 250 fg/assay
11	10 spiked tubes: CT 0 fg/assay – GC 2500 fg/assay
12	10 spiked tubes: CT 0 fg/assay – GC 250,000 fg/assay
13	12 tubes: CT 0 fg/assay – GC 0 fg/assay

b. *Linearity/assay reportable range:* NA

RLU levels cannot be compared because the kinetic algorithm moderates interpretation

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

Controls are prepared in-house by the manufacturer and are not traceable to a standard or independent measure.

d. *Detection limit:*

A study was performed with CT and NG RNA spiked into negative vaginal and PC sample polls at 5 fg and 250 fg/assay. 60 replicates of each were tested on the Tigris DTS System. Similarities in detection limits cannot be deduced from this study. Using this model, the actual LoD for neither Tigris nor semi-manual DTS can be assessed, and comparison is not possible. One can conclude that testing at this level of RNA (the amount in the provided controls) is reproducible with >95% confidence. The labeling does not infer limits of detection with these data.

The following limitation (that would apply to both DTS and Tigris testing with AC2 on PreservCyt samples was added to the AC2 labeling:

“There is no evidence of degradation of nucleic acids in PreservCyt solution. If a PreservCyt specimen has small numbers of CT and GC cellular material, uneven distribution of this cellular material may occur. Also, when compared to direct sampling with the Aptima Swab Transport Media, the additional volume of PreserCyt Solution results in greater dilution of the sample material. These factors may affect the ability to detect small numbers of organisms in the collected material. If negative results from the specimen do not fit with the clinical impression, a new specimen may be necessary.”

e. *Analytical specificity:*

Culture isolates were added to PreservCyt liquid Pap Media at approximately 10E6 cells/mL and tested on the Tigris DTS System. *C. pneumoniae* and *C. psittaci* (2 strains)

were also tested. As seen previously with Tigris DTS data, RLU levels with *N. elongata* in PreservCyt solution were increased (21-41 RLU vs 3-7 RLU for the majority of other organisms tested). This same effect was observed with the same organism in Swab Transport Media (k032194).

Additionally, 235 vaginal swab specimens (in STM) and 240 negative post-processed Cytoc specimens were tested for inhibition by adding 5 fg CT RNA and 250 fg GC RNA per assay. No AC2 results were inhibitory for this level of added RNA.

With addition of fresh blood (10% v/v) to 3 clinical vaginal swab and 3 post-processed Cytoc specimen pools that were spiked with 5 fg CT RNA and 250, no differences in result between DTS and Tigris were observed for pools with and without blood, or for RNA-spiked pools with and without blood.

f. Assay cut-off:

The AC2 kinetic profiles were modified with the Tigris application (k032194). Although the cutoffs measured in RLUs 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).

2. Comparison studies: Clinical specimens obtained from 6 cytopathology laboratories were processed at two laboratories and transferred with up to 3 Aptima specimen transfer kit tubes. One vaginal swab was obtained from some women. All specimens were shipped to GenProbe and initially tested with the AC2 assay using DTS instrumentation (semi-automated) to separate positive specimens for comparing results between Tigris and DTS methods for the AC2 with vaginal swab and PreservCyt collected samples. Selected specimens (170 vaginal swabs and 170 processed PreservCyt specimens) from 181 women were for tested on AC2 – Tigris instrumentation. Specimens from 309 women were used to prepare specimen pools used for a clinical panel of RNA-spiked samples. Any specimen with invalid or equivocal AC2 results on DTS instrumentation was excluded. Of the 17 worklists initiated on the Tigris, 13 (76%) were valid and 4 were invalid runs (due to luminometer high background that were repeated).

a. Method comparison with predicate device: With the pre-selected specimens, agreement of Tigris results for vaginal swab specimens ranged from 96% to 100% for all result combinations (CT+GC+, CT+GC-, CT-GC+, and CT-GC-). Agreement for PreservCyt specimens ranged from 96% to 100%.

b. Matrix comparison: No differences in agreement between semi-automated DTS and Tigris DTS system were observed for the two matrices evaluated (vaginal swabs in specimen transport media and endocervical samples in processed PreservCyt added to STM).

3. Clinical studies:

a. Clinical Sensitivity: NA

b. Clinical specificity: NA

4. Clinical cut-off: NA

5. Expected values/Reference range: NA

N. Instrument Name: Tigris DTS™ System

O. System Descriptions:

1. Modes of Operation: no change

2. Software: Current software version is 3.3.13; changes to initial release version (1.04.04) include bug fixes, luminometer performance check enhancements, language handling for Tigris installation SW, Sample temperature monitoring improvements, UPS enhancements and other minor improvements. Target Capture Reagent pipetting parameters (part of the Assay Definitions Module) were changed to increase the pipetting time. Changes were made to aspirate and dispense specimen several times, allowing for sufficient volume aspiration and dispensing.

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

Yes in k032194

3. Specimen Identification: no change

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). Residual endocervical samples from ThinPrep 2000 processing must be transferred to Specimen Collection tubes with using an ancillary Specimen Transfer Kit. Specimen tubes are placed into racks containing 20 tubes each. The tubes must be visually checked for adequate volume and precipitates.

5. Calibration: no change

6. Quality Control: Assay controls are RNA preparations that would not monitor factors associated with matrix in the test system; users must prepare controls from cultured material, or use previously positive specimen material.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Carryover studies previously showed that low levels of contamination (falsely positive or equivocal in blank samples) could be expected (up to 2% on one of three instruments evaluated). Warnings are included in the package insert to advise laboratories. This rate most likely due to carry-over would be higher than expected prevalence in many populations.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

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