510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K180681

B. Purpose for Submission:

To obtain clearance for an additional specimen type, female urine on Aptima Combo 2 Assay (Panther System)

C. Measurand:

Chlamydia trachomatis (CT) and/or *Neisseria gonorrhoeae* (GC) ribosomal RNA (rRNA)

D. Type of Test:

Nucleic acid amplification assay

E. Applicant:

Hologic, Inc.

F. Proprietary and Established Names:

Aptima Combo 2 Assay (Panther System)

G. Regulatory Information:

1. Regulation section:

   21 CRF 866.3390, *Neisseria* spp. direct serological test reagents

2. Classification:

   Class II

3. Product code:

   LSL: DNA-Reagents, Neisseria
   MKZ: DNA Probe, Nucleic Acid Amplification, Chlamydia

4. Panel:

Microbiology (83)

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* (CT) and/or *Neisseria gonorrhoeae* (GC) to aid in the diagnosis of chlamydial and/or gonococcal urogenital disease using the Panther System as specified.

   On the Panther System, the assay may be used to test the following specimens from symptomatic and asymptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens, clinician-collected gynecological specimens collected in the PreservCyt Solution, patient-collected vaginal swab specimens,[1] and female and male urine specimens.

   [1]Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The vaginal and multitest swab specimen collection kits are not for home use.

2. Indication(s) for use:

   Same as Intended Use.

3. Special conditions for use statement(s):

   For Prescription Use

4. Special instrument requirements:

   Panther System

I. Device Description:

The Aptima Combo 2 Assay is a target amplification nucleic acid probe test that utilizes target capture, transcription mediated amplification, and dual kinetic assay technologies for the *in vitro* qualitative detection and differentiation of rRNA from CT and/or GC to aid in the diagnosis of chlamydial and/or gonococcal urogenital disease using the Panther System.

The current Aptima Combo 2 Assay is similar to the APTIMA Combo 2 Assay originally cleared (K111409) for use on the Panther System. There are no changes to the APTIMA Combo 2 Assay (Panther System) catalog numbers (303094 and 302923), accessories, or ancillary kits. The 'Aptima Urine Specimen Collection Kit for Male and Female Urine Specimens' (catalog number 301040) cleared for use with the cleared Aptima Combo 2 Assay on the DTS System (K003395), TIGRIS System (K032194), and Panther System (K132251) is required to collect the female urine specimens.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Aptima Combo 2 Assay (Panther System)

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

   K132251

3. Comparison with predicate:

Table 1: Similarities between Predicate Device and Aptima Combo 2 Assay (Panther System)

Similarities		
Item	**Predicate Device**	**Subject Device**
	Aptima Combo 2 Assay (Panther System) (K132251)	**Aptima Combo 2 Assay (Panther System) (K180681)**
Regulation	866.3390	866.3390
Device Class	II	II
Technology/ Detection	Target Capture (TC), Transcription-mediated Amplifiction (TMA), Hybridization Protection Assay (HPA)	Same
Assay Targets	*Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (GC) rRNA	Same
Assay Results	Qualitative	Same
Instrument System	Panther System	Same

Table 2: Differences Between Predicate Device and Aptima Combo 2 Assay (Panther System)

Differences		
	Predicate Device	**Subject Device**
Item	**Aptima Combo 2 Assay (Panther System) (K132251)**	**Aptima Combo 2 Assay (Panther System) (K180681)**
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* (CT) and/or *Neisseria gonorrhoeae* (GC) to aid in the diagnosis of chlamydial and/or gonococcal urogenital disease using the Panther System as specified. On the Panther System, the assay may be used to test the following specimens from symptomatic and asymptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens, clinician-collected gynecological specimens collected in the PreservCyt Solution, patient-collected vaginal swab specimens[1] and male urine specimens. [1]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.	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* (CT) and/or *Neisseria gonorrhoeae* (GC) to aid in the diagnosis of chlamydial and/or gonococcal urogenital disease using the Panther System as specified. On the Panther System, the assay may be used to test the following specimens from symptomatic and asymptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens, clinician-collected gynecological specimens collected in the PreservCyt Solution, patient-collected vaginal swab specimens,[1] and female and male urine specimens. [1]Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The vaginal and multitest swab specimen collection kit is not for home use.
Specimen Types	Female specimens: • Vaginal swab • Endocervical swab • Gynecological specimens in PreservCyt solution Male Specimens: • Urethral Swab • Urine	Female specimens: • Vaginal swab • Endocervical swab • Gynecological specimens in PreservCyt solution • Urine Male Specimens: • Urethral Swab • Urine

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

Not applicable

L. Test Principle:

The Aptima Combo 2 Assay utilizes target capture, transcription-mediated amplification, hybridization protection assay, and dual kinetic assay for specimen processing, amplify target rRNA, and detect aplicon respectively. Please refer to the decision summaries of K111409 and K132251 for detailed description.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility and within laboratory precision studies were previously reviewed and described in K132251 and K111409.

b. Linearity/assay reportable range:

Not Applicable; this is a qualitative assay.

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

Specimen stability and controls were previously reviewed and described in K132251 and K111409.

d. Detection limit:

Limit of detection study was previously reviewed and described in K132251 and K111409.

e. Analytical specificity:

Please refer to the decision summary of K111409 for the cross-reactivity data.

f. Carryover study:

Carryover study was previously reviewed and described in K132251 and K111409.

g. Assay cut-off:

Assay cut-off was previously reviewed and described in K132251 and K111409.

2. Comparison studies:

   a. *Method comparison with predicate device:*

      Not applicable.

   b. *Matrix comparison:*

      Not applicable.

3. Clinical studies:

   The clinical perofrmance of the Aptima Combo 2 Assay with female urine specimens was evaluated against a composite comparator algorithm (CCA) comprised of three FDA-cleared nucleic acid amplification tests (NAATs). A subject was considered positive if two out of three comparator NAATs were positive. The subject was considered negative if two out of three NAATs were negative. CCA result was determined for CT and GC using urine test results from upto three FDA-cleared CT/GC NAATs. The clinical data from a previously completed prospective clinical study was renalayzed and the remnant female urine samples were tested by a third FDA-cleared NAAT (tie-breaker) if the first two comparator NAAT results for urine samples did not determine the CCA result.

   A total of 2640 women (symptomatic and asymptomatic) were enrolled from 17 geographically and ethically diverse US clinical sites. Of the 2640 subjects enrolled, 42 subjects were withdrawn. Of the 2598 non-withdrawn subjects, 2581 subjects were tested with the Aptima Combo 2 assay (Panther System) while 17 subjects had urine samples withdrawn or not collected, i.e., missing both CT and GC results from Aptima Combo 2 Assay (Panther System). Samples with initially invalid, equivocal, or error results were retested. All 2581 samples had final valid results after required retesting. One out of 2581 samples had a repeat CT equivocal result (negative GC result) and one sample had a repeat GC equivocal result (negative CT result). Of the 2581 subjects that had valid Aptima Combo 2 Assay (Panther System) results, 2580 subjects had a conclusive CT and/or GC CCA result and were evaluable for performance analyses; one subject had unknown CCA result for both CT and GC. Demographics of the 2580 evaluable subjects are presented in Table 3.

Table 3: Summary of Evaluable Subjects Stratified by Subject Symptom Status and Age

	N (%)
Total	2580 (100)
Symptom Status	
Asymptomatic	1196 (46.4)
Symptomatic	1384 (53.6)
Age Group	
16 to 17 years	47 (1.8)
18 to 20 years	346 (13.4)
21 to 30 years	1350 (52.3)
31 to 40 years	550 (21.3)
>40 years	287 (11.1)

Of the 2580 evaluable subjects, 2572 subjects had a conclusive CT CCA result and were evaluable for performance analyses for CT detection (including one with equivocal result with Aptima Combo 2 Assay). The remaining eight subjects had an unknown composite comparator status. Of the 2580 evaluable subjects, 2579 subjects had a conclusive GC CCA result and were evaluable for performance analyses for GC detection (including one with equivocal result with Aptima Combo 2 Assay). The remaining one subject had an unknown composite comparator status.

Results from female urine samples with the Aptima Combo 2 Assay (Panther system) were compared to the CCA results to establish the positive percent agreement (PPA) and negative percent agreement (NPA). Samples with final equivocal results were included in the performance analyses and categorized as false negative relative to the CCA result. Additionally, results in urine samples by Aptima Combo 2 Assay (Panther System) were also compared with the vaginal and endocervical swab specimens using the patient infected status (PIS) algorithm. In the Clinical Study, the Aptima Combo 2 Assay detected 8.3% fewer CT infections in female urine than in vaginal and endocervical swab specimens and 12.9% fewer GC infections than in vaginal swab specimens and 15.2% fewer GC infections than in endocervical swab specimens when compared to PIS algorithm.

Tables 4 and 5 show the PPA and NPA of the Aptima Combo 2 Assay for CT and GC detection based on the CCA in female urine samples.

Table 4: Performance Characteristics of the Aptima Combo 2 Assay for CT detection in Female Urine Samples

Specimen Type[1]	Symptom Status	n	CCA+ AC2+	CCA- AC2+	CCA- AC2-	CCA+ AC2-	PPA % (95% CI)[3]	NPA % (95% CI)[3]
FU	Sym	1379	109	2[4]	1267[5]	1	99.1 (95.0-99.8)	99.8 (99.4-100)
	Asym	1193	65	3[6]	1124[7]	1[2]	98.5 (91.9-99.7)	99.7 (99.2-99.9)
	Overall	2572	174	5	2391	2[2]	98.9 (96.0-99.7)	99.8 (99.5-99.9)

AC2 = Aptima Combo 2 Assay, Asym = asymptomatic, CCA = composite comparator algorithm, CI = confidence interval, FU = female urine, NPA = negative percent agreement, PPA = positive percent agreement, Sym = symptomatic.

1 Symptomatic and asymptomatic female urine sample results are from Clinical Study 3.

2 Includes equivocal results from Panther AC2 testing. Equivocal results from AC2 testing are considered indeterminate; a new specimen should be collected.

3 Score CI.

4 2/2 subjects had positive CT vaginal swab sample results in both reference NAATs.

5 38/1267 subjects had at least one positive CT vaginal swab sample result by a reference NAAT; one or more vaginal swab sample reference results were not available 11/1267 subjects; 1218/1267 subjects had negative vaginal swab sample reference results.

6 1/ 3 subject had positive CT vaginal swab sample results in both reference NAATs; 2/3 subjects had negative vaginal swab sample reference results.

7 20/1124 subjects had at least one positive CT vaginal swab sample result by a reference NAAT; one or more vaginal swab sample reference results were not available for 11/1124 subjects; 1093/1124 subjects had negative vaginal swab sample reference results.

Table 5: Performance Characteristics of the Aptima Combo 2 Assay for GC detection in Female Urine Samples

Specimen Type[1]	Symptom Status	n	CCA+ AC2+	CCA- AC2+	CCA- AC2-	CCA+ AC2-[2]	PPA % (95% CI)[3]	NPA % (95% CI)[3]
FU	Sym	1383	19	0	1363[4]	1	95.0 (76.4-99.1)	100 (99.7-100)
	Asym	1196	9	0	1187[5]	0	100 (70.1-100)	100 (99.7-100)
	Overall	2579	28	0	2550	1	96.6 (82.8-99.4)	100 (99.8-100)

AC2 = Aptima Combo 2 Assay, Asym = asymptomatic, CCA = composite comparator algorithm, CI = confidence interval, FU = female urine, NPA = negative percent agreement, PPA = positive percent agreement, Sym = symptomatic.

1 Symptomatic and asymptomatic female urine sample results are from Clinical Study 3.

2 Includes equivocal results from Panther AC2 testing. Equivocal results from AC2 testing are considered indeterminate; a new specimen should be collected.

3 Score CI.

4 5/1363 subjects had at least one positive GC vaginal swab sample result by a reference NAAT; one or more vaginal swab sample reference results were not available for 11/1363 subjects; 1347/1363 subjects had negative vaginal swab sample reference results.

5 6/1187 subjects had at least one positive GC vaginal swab sample result by a reference NAAT; one or more vaginal swab sample reference results were not available for 11/1187 subjects; 1170/1187 asymptomatic subjects had negative vaginal swab sample reference results.

Although the 95% confidence interval (CI) for GC PPA was wide, point estimates were 95% for symptomatic subjects and >95% for asymptomatic subjects, with an overall agreement >95%. Furthermore, very high agreement was observed between Aptima Combo 2 assay (Panther System) and CCA result for the detection of CT in female urine samples. Therefore, the performance of Aptima Combo 2 Assay (Panther System) based on the CCA in female urine specimens was acceptable.

4. Clinical cut-off**:**

   Not applicable

5. Expected values/Reference range:

   The positivity rate of CT observed with Aptima Combo 2 Assay (Panther System) during this multi-site Clinical Study 3 was 7.1% overall. The overall positivity rate of GC observed with Aptima Combo 2 Assay (Panther System) was 1.1%.

N. Instrument Name:

Panther System

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ____X____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No ___X____

2. Software:

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

   Yes ___X____ or No _____

3. Specimen Identification:

   By handheld barcode reader and positional checks.

4. Specimen Sampling and Handling:

   Fully automated.

5. Calibration:

   Hologic, Inc Field Service Engineers perform a luminometer calibration on the Panther System every 12 months as part of the Preventive Maintenance. Additionally, there are process controls and calibration checks on all of the dispensers, thermal devices, and the vacuum system.

6. Quality Control:

   In addition to the assay controls that are specific to each assay, the Panther System contains process controls that employ both hardware and software components. The process controls include, but are not limited to:

   - Verification that the sequence of assay processing steps is correct for each reaction.
   - Verification that the reaction incubation times and temperatures are correct.
   - Verification that reagents and fluids are appropriately dispensed.

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

Not applicable

Q. Proposed Labeling:

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

R. Conclusion:

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