May 17, 2020

Hologic, Inc.
Anila Tarte
Regulatory Affairs Specialist
10210 Genetic Center Drive
San Diego, California 92121

Re: K200866
Trade/Device Name: Aptima Combo 2 Assay (Panther System) and Aptima Combo 2 Assay (Tigris System)
Regulation Number: 21 CFR 866.3393
Regulation Name: Nucleic Acid Detection System for Non-Viral Microorganism(s) Causing Sexually Transmitted Infections.
Regulatory Class: Class II
Product Code: QEP, LSL, MKZ
Dated: March 30, 2020
Received: April 1, 2020

Dear Anila Tarte:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or post-marketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Steven Gitterman, M.D., Ph.D.
Deputy Director
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

510(k) SUMMARY

Aptima Combo 2® Assay (Panther® and Tigris® DTS® System)

I. SUBMITTER

Hologic, Inc.
10210 Genetic Center Drive
San Diego, CA 92121

Contact Information:

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Date Prepared: May 14, 2020

II. DEVICES

Proprietary Name:	Aptima Combo 2® Assay (Panther® System)
Classification Name:	Nucleic Acid Detection System for Non-Viral Microorganism(s) Causing Sexually Transmitted Infections
Regulation Number:	866.3393
Regulatory Class:	Class II
Product Code:	QEP
Subsequent Product Code:	MKZ, LSL

Proprietary Name:	Aptima Combo 2® Assay (Tigris® DTS® System)
Classification Name:	Nucleic Acid Detection System for Non-Viral Microorganism(s) Causing Sexually Transmitted Infections
Regulation Number:	866.3393
Regulatory Class:	Class II
Product Code:	QEP
Subsequent Product Code:	MKZ, LSL

III. PREDICATE DEVICE

The predicate device is the Aptima Combo 2 Assay on Panther and Tigris Systems (K200436; cleared 03/24/2020). The predicate device has not been subject to a design-related recall.

IV. DEVICE DESCRIPTIONS

The Aptima Combo 2 Assay combines the technologies of target capture, TMA, and DKA. Specimens are collected and transferred into their respective specimen transport tubes. The transport solutions in these tubes release the rRNA targets and protect them from degradation during storage. When the Aptima Combo 2 Assay is performed in the laboratory, the target rRNA molecules are isolated from specimens by use of capture oligomers via target capture that utilizes magnetic microparticles. The capture oligomers contain sequences complementary to specific regions of the target molecules as well as a string of deoxyadenosine residues. A separate capture oligomer is used for each target. During the hybridization step, the sequence specific regions of the capture oligomers bind to specific regions of the target molecules. The capture oligomer:target complex is then captured out of solution by decreasing the temperature of the reaction to room temperature. This temperature reduction allows hybridization to occur between the deoxyadenosine region on the capture oligomer and the poly-deoxythymidine molecules that are covalently attached to the magnetic particles. The microparticles, including the captured target molecules bound to them, are pulled to the side of the reaction vessel using magnets and the supernatant is aspirated. The particles are washed to remove residual specimen matrix that may contain amplification reaction inhibitors. After the target capture steps are completed, the specimens are ready for amplification.

Target amplification assays are based on the ability of complementary oligonucleotide primers to specifically anneal and allow enzymatic amplification of the target nucleic acid strands. The Aptima Combo 2 Assay replicates a specific region of the 23S rRNA from CT and a specific region of the 16S rRNA from GC via DNA intermediates. A unique set of primers is used for each target molecule. Detection of the rRNA amplification product sequences (amplicon) is achieved using nucleic acid hybridization. Single-stranded nucleic acid chemiluminescent probes, which are complementary to a region of each target amplicon, are labeled with different acridinium ester molecules. The updated version of the Aptima Combo 2 assay incorporates a

second CT probe, complementary to a unique region of the existing CT amplicon. This tandem probe provides detection coverage for the variant strains of *C. trachomatis* that emerged in 2019. The labeled probes combine with amplicon to form stable hybrids. The Selection Reagent differentiates hybridized from unhybridized probe, eliminating the generation of signal from unhybridized probe. During the detection step, light emitted from the labeled hybrids is measured as photon signals in a luminometer, and are reported as Relative Light Units (RLU). In DKA, differences in the kinetic profiles of the CT and GC labeled probes allow for the differentiation of signal; kinetic profiles are derived from measurements of photon output during the detection read time. The chemiluminescent detection reaction for CT signal has very rapid kinetics and has the "flasher" kinetic type. The chemiluminescent detection reaction for GC signal is relatively slower and has the "glower" kinetic type. Assay results are determined by a cut-off based on the total RLU and the kinetic curve type.

V. DESCRIPTION OF DEVICE MODIFICATION

The clearance of this Special 510(k) application supports a change in formulation to the Probe reagent contained in the Aptima Combo 2 assay. Reformulation of the Probe reagent was necessary to detect recently emerged variants of *Chlamydia trachomatis* (CT) that were discovered outside of the U.S. using the Panther System or Tigris System. The updated version of the Aptima Combo 2 Assay (termed "updated AC2 assay") includes dual (redundant) CT detection probe, which not only identifies all recent variants of CT, but is also intended to provide diagnostic protection against future genetic variants within the AC2 probe region.

Table 1: Aptima Combo 2 Assay - Catalog Numbers

Kit Description	Current Kit Cat. No.	Updated Kit Cat. No.
Aptima Combo 2 Assay, 100-Test Kit (Panther System)	302923	PRD-05576
Aptima Combo 2 Assay, 250-Test Kit (Panther System)	303094	PRD-05571
Aptima Combo 2 Assay, 250-Test Kit (Tigris System)	301130	PRD-05572
Aptima Combo 2 Assay, 1000-Test Kit (Tigris System) *	301130B	PRD-05572B

* AC2 for Tigris 1000-Test Kit is packaged to contain four 250-Test Kits

VI. INDICATIONS FOR USE

Intended Use - Aptima Combo 2 Assay (Panther)

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 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, PreservCyt® Solution liquid Pap specimens, vaginal, throat, rectal, and male urethral swab specimens; 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 Aptima Multitest Swab Specimen Collection Kit has not been evaluated for home use.

Intended Use - Aptima Combo 2 Assay (Tigris)

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 Tigris® DTS® Automated Analyzer or semi-automated instrumentation as specified. The assay may be used to test the following specimens from symptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens; and female and male urine specimens. The assay may be used to test the following specimens from asymptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens; patient-collected vaginal swab specimens[1]; and female and male urine specimens. The assay is also intended for use with the testing of gynecological specimens, from both symptomatic and asymptomatic patients, collected in the PreservCyt® Solution.

[1]Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The Aptima Multitest Swab Specimen Collection Kit is not for home use.

VII. COMPARISON OF TECHNOLOGICAL CHARACTERISTICS WITH THE PREDICATE DEVICES

A comparison of the subject device to the predicate devices is summarized in **Table 2** (AC2 assay on Panther) and **Table 3** (AC2 assay on Tigris). Use of the updated AC2 assay does not change the principles of procedure, intended use, or primary technological characteristics. The similarities and differences between the subject and predicate devices are further discussed following the substantial equivalence tables. This discussion is the same for each assay.

Table 2: Comparison Between Predicate Device and Subject Device - AC2 Assay on the Panther System

Item	**Predicate Device AC2 Assay (Panther) K200436**	**Subject Device AC2Assay (Panther) K200866**
Technology Principle of Operation	Target Capture (TC), Transcription-Mediated Amplification (TMA), Hybridization Protection Assay (HPA)	Same
Platform	Automated Panther System	Same
Function	Detection and differentiation of rRNA from *Chlamydia trachomatis* and *Neisseria gonorrhoeae*	Same
Organisms Detected	*Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (GC)	Same
Patient Population	Symptomatic and asymptomatic individuals	Same
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, throat, rectal, and male urethral swab specimens, clinician-collected gynecological	Same* 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 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, PreservCyt® Solution liquid pap specimens, vaginal, throat,

Item	Predicate Device AC2 Assay (Panther) K200436	Subject Device AC2Assay (Panther) K200866
	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 Aptima Multitest Swab Specimen Collection Kits have not been evaluated for home use.	rectal, and male urethral swab specimens, 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 Aptima Multitest Swab Specimen Collection Kit has not been evaluated for home use.

* Edits to the intended use were made for clarification purposes only. Specimen types were aligned and/or grouped into respective clinician-collected and patient-collected specimen types

Table 3: Comparison Between Predicate Device and Subject Device – AC2 Assay on the Tigris System

Item	Predicate Device AC2 Assay (Tigris) K200436	Subject Device AC2 Assay (Tigris) K200866
Technology Principle of Operation	Target Capture (TC), Transcription-Mediated Amplification (TMA), Hybridization Protection Assay (HPA)	Same
Platform	Automated Tigris System	Same
Function	Detection and differentiation of rRNA from *Chlamydia trachomatis* and *Neisseria gonorrhoeae*	Same
Organisms Detected	*Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (GC)	Same
Patient Population	Symptomatic and asymptomatic individuals	Same
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 Tigris® DTS® Automated Analyzer. On the Tigris DTS system, the assay may be used to test the following specimens from symptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens; and female and male urine specimens. The assay may be used to test the following specimens from asymptomatic individuals: clinician-collected endocervical, vaginal and male urethral swab specimens; patient-collected vaginal swab specimens[1]; and female and	Same

Item	Predicate Device AC2 Assay (Tigris) K200436	Subject Device AC2 Assay (Tigris) K200866
	male urine specimens. The assay is also intended for use with the testing of gynecological specimens, from both symptomatic and asymptomatic patients, collected in the PreservCyt® Solution. [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.	

Similarities

Both the predicate and subject devices utilize the same technology and principles of operation, mechanisms of action, and run on the same automated instrument systems. There are no changes to the assay kit configuration, intended use, results interpretation, or existing performance of the assay. Additionally, the proposed changes do not affect the existing Aptima Controls Kit, Aptima ancillary or collection kits, or the software and hardware associated with the use of the Panther or Tigris systems.

Differences

Changes to the user interface are minimal and include updated packaging and labeling to differentiate between the current AC2 assay kit and the updated AC2 assay kit. Package insert changes include new kit catalog numbers and updates to the Analytical Performance section demonstrating detection of all recent CT variants using the updated AC2 assay.

VIII. Design Control Activities

Hologic's overall product development activities are conducted per procedure, 'Product Development Procedure' which is in conformance with the design control requirements as specified in 21 CFR 820.30. Verification testing was performed to confirm clinical comparability between the current Probe and reformulated Probe reagents. The completed verification studies demonstrate that the reformulated Probe reagent does not impact assay performance, assay safety and effectiveness, and confirms that the modified assay meets the design input requirements.

Hologic risk analysis activities are conducted per Product Safety Risk Management Procedure which is in conformance with ISO 14971:2007. Based on the results of the risk analysis and verification activities, and in accordance with ISO 14971:2007, all risks are reduced as far as possible and meet the pre-defined acceptability criteria. There were no hazards that fell within the "Undesirable" or "Unacceptable" residual risk regions. The device modifications do not introduce any new hazards or increase the overall residual risk as compared to the currently marketed products.

IX. ASSAY PERFORMANCE

Performance of the updated AC2 Assay was evaluated. The result of this evaluation demonstrated that existing performance and claims of the assay were not impacted due to the reformulated Probe reagent.

Brief Description of Non-Clinical Data

The following analytical (non-clinical) studies were conducted to support the clearance of the updated AC2 assay on the Panther System and Tigris System.

Limit of Detection – Panther and Tigris

The analytical sensitivity for the Finnish variant of *Chlamydia trachomatis* (FI-nvCT) was determined by testing dilutions of *in vitro* transcripts in negative urine specimens, negative ThinPrep specimens, and simulated swab matrix specimens. Thirty replicates of each dilution were tested on both the Panther system and Tigris system with each of three reagent lots of the updated AC2 assay for a total of 90 replicates per specimen type. The analytical sensitivity was determined to be less than one IFU per assay in urine, ThinPrep, and simulated swab matrix specimens. The detection capabilities of the updated version of the AC2 assay were confirmed across multiple CT variants.

Clinical Comparability

The clinical specimen agreement between the current version and updated version of the AC2 assay was evaluated using remnant swab specimens collected from patients undergoing CT

and/or GC screening. A single replicate of each specimen was tested with both the current version and the updated version of the AC2 assay on the Panther System.

Table 4 and **Table 5** show clinical comparison results for the CT and GC positive and negative percent agreement, respectively. The overall agreement was >99.0% for both CT and GC.

Table 4: Clinical Specimen Comparison Results - CT

		Current AC2 Assay	
		CT Positive	**CT Negative**
Updated AC2 Assay	**CT Positive**	49	3
	CT Negative	0	273
Positive Percent Agreement (95% C.I.): 100% (92.7% - 100%)			
Negative Percent Agreement (95% C.I.): 98.9% (96.9% - 99.6%)			

Table 5: Clinical Specimen Comparison Results - GC

		Current AC2 Assay	
		GC Positive	**GC Negative**
Updated AC2 Assay	**GC Positive**	47	1
	GC Negative	0	275
Positive Percent Agreement (95% C.I.): 100% (92.4% - 100%)			
Negative Percent Agreement (95% C.I.): 99.6% (98.0% - 99.9%)			

CT/GC Clinical Sample Agreement

The clinical panel agreement study evaluated the equivalence between the current and updated versions of the AC2 assay using 20 prepared CT/GC clinical panels containing 0 to 2,500 IFU/mL of wild type CT, 0 to 500 IFU/mL of FI-nvCT, and 0 to 125,000 CFU/mL of GC in urine specimens. Each of the 20 panels were tested in triplicate in two runs per day, on three Panther systems, by two operators, using three lots of reagents over seven days.

The results show 100% (97.6-100%) total CT and GC agreement to the expected panel result for the updated AC2 assay. Results also show 100% (97.6-100%) total CT and GC agreement to the expected panel result for the current AC2 assay, with the exception of the moderate (0.2 IFU/mL) FI-nvCT only panel, which had 98.2% (93.5-99.5%) CT agreement and 99.1% (94.9-99.8%) GC agreement. The percent agreement to the expected result for the detection of wild

type CT and GC is comparable between the current AC2 assay and the updated AC2 assay. In addition, the observed variability of the current AC2 and the updated AC2 assays was comparable between instruments, lots, operators, days, and runs.

Microorganism Cross-Reactivity and Microbial Interference

The analytical specificity and microbial interference of the updated version of the AC2 assay was evaluated using 86 microorganisms consisting primarily of viral, bacterial, and yeast strains. Each pool of microorganisms was tested with and without the presence of FI-nvCT *in vitro* transcripts at a concentration of 3x LoD. None of the microorganisms tested were found to have an impact on the detection capabilities or analytical specificity of the updated version of the AC2 assay.

Table 6: Cross-Reactivity Microorganisms

Pool ID	Microorganism	Pool ID	Microorganism
0	SVSM (Control)		
1	*Acinetobacter lwoffii*	12	*Proteus vulgaris*
	Actinomyces israelii		*Shigella dysenteriae*
	Alcaligenes faecalis		*Shigella flexneri*
	Anaerococcus vaginalis		*Shigella sonneri*
2	*Arcanobacterium haemolyticum*	13	*Stenotrophomonas maltophilia*
	Atopobium vaginae		*Streptococcus agalactiae*
	Bacteroides fragilis		*Streptococcus anginosus*
	Bacteroides oralis		*Streptococcus pyogenes*
3	*Bifidobacterium adolescentis*	14	*Ureaplasma parvum*
	Bordatella parapertussis		*Ureaplasma urealyticum*
	Campylobacter jejuni		*Veillonella parvula*
	Campylobacter rectus		*Burkholderia cepacia*
4	*Citrobacter koseri*	15	*Clostridium difficile*
	Corynebacterium diptheria		*Prevotella bivia*
	Corynebacterium genitalium		Candida albicans
	Corynebacterium pseudodiptheriticum		Cryptococcus neoformans
5	*Eggerthella lenta*	16	Entamoeba histolytica
	Enterobacter cloacae		Giardia lamblia
	Enterococcus faecalis		Pentatrichomonas hominis
	Escherichia coli		Trichomonas vaginalis

Pool ID	Microorganism	Pool ID	Microorganism
6	*Fusobacterium necrophorum*	17	Adenovirus Type 07A
	Fusobacterium nucleatum		Coronavirus 229E
	Gardnerella vaginalis		Coxsackievirus B3
	Helicobacter pylori		Echovirus Type 11
7	*Haemophilus ducreyi*	18	Enterovirus Type 68
	Haemophilus parahaemolyticus		Epstein-Barr virus
	Haemophilus parainfluenzae		Hepatitis B Virus
	Klebsiella pneumoniae		Hepatitis C Virus
8	*Lactobacillus acidophilus*	19	HIV
	Legionella (Tatlockia) micdadei		HPV 16 (SiHa cells)
	Legionella jordanis		HPV 18 (HeLa cells)
	Leptotrichia buccalis		Human Metapneumovirus Type 20
9	*Listeria monocytogenes*	20	HSV I
	Megasphaera Type 1		HSV II
	Mobiluncus curtisii		Influenza A H3N2
	Moraxella catarrhalis		Influenza B Massachusetts/2/12
10a	*Mycoplasma genitalium*	21	Norovirus Group II
	Mycoplasma hominis		Respiratory Syncytial virus Type B
	Mycoplasma pneumoniae		Rhinovirus A16
10b	*Neisseria gonorrhoeae*	22	*Chlamydia pneumoniae*
11	*Peptostreptococcus micros*		*Chlamydia psittaci*
	Propionibacterium acnes		*Chlamydia psittaci*
	Staphylococcus aureus		
	Staphylococcus epidermidis		

X. CONCLUSIONS

A comparison of the intended use, technological characteristics, and results from the analytical performance studies demonstrate that the updated AC2 assay on the Panther and Tigris systems performs comparably to the predicate device.