



Food and Drug Administration  
10903 New Hampshire Avenue  
Document Control Center – WO66-G609  
Silver Spring, MD 20993-002

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10210 Genetic Center Drive  
San Diego, CA 92121-4362

OCT 12 2012

Re: P120007  
APTIMA<sup>®</sup> HPV 16 18/45 Genotype Assay  
Filed: April 19, 2012  
Amended: June 19, 2012; July 26, 2012  
Procode: OYB, NSU

Dear Ms. Godfredsen:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the APTIMA HPV 16 18/45 Genotype Assay.

APTIMA HPV 16 18/45 Genotype Assay Indications for Use:

The APTIMA HPV 16 18/45 Genotype Assay is an *in vitro* nucleic acid amplification test for the qualitative detection of E6/E7 viral messenger RNA (mRNA) of human papillomavirus (HPV) types 16, 18, and 45 in cervical specimens from women with APTIMA HPV Assay positive results. The APTIMA HPV 16 18/45 Genotype Assay can differentiate HPV 16 from HPV 18 and/or HPV 45, but does not differentiate between HPV 18 and HPV 45. Cervical specimens in ThinPrep Pap Test vials containing PreservCyt Solution and collected with broom-type or cytobrush/spatula collection devices\* may be tested with the APTIMA HPV 16 18/45 Genotype Assay. The assay is used with the TIGRIS DTS System.

The use of the test is indicated:

1. In patients 21 years and older with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results, the APTIMA HPV 16 18/45 Genotype Assay can be used to test samples from women with APTIMA HPV Assay positive results to assess the presence or absence of high-risk HPV genotypes 16, 18, and/or 45. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy.
2. In women 30 years and older, the APTIMA HPV 16 18/45 Genotype Assay can be used to test samples from women with APTIMA HPV Assay positive results. The assay results will

be used in combination with cervical cytology to assess the presence or absence of high-risk HPV genotypes 16, 18, and/or 45. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

\* Broom-type device (e.g., Wallach Pipette), or endocervical brush/spatula.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at nine months for the APTIMA HPV 16 18/45 Genotype Assay when stored at 2 - 8°C, with the exception of the subset of reagents in the APTIMA HPV 16 18/45 Genotype Room Temperature Box, which should be stored at 15 - 30°C. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" (please use this title even if the specified interval is more frequent than one year) and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study reports (PAS) to establish the long term performance of APTIMA HPV 16 18/45 Assay, as described below:

A study must be conducted as per approved protocol No. HPVGTS-US10-002 located in P120007 Volume 7, Appendix 7-04. This study will continue the follow-up of study subjects enrolled in

the premarket Adjunct Study arm for the APTIMA HPV Assay TIGRIS System. Women who are 30 years and older with cytology-negative (negative for intraepithelial lesion or malignancy; NILM) results at routine screening (baseline), and who may have undetected cervical disease (cervical intraepithelial neoplasia [CIN] grade 2 or more severe;  $\geq$ CIN2) will continue to be followed out to three years. The objective of the post-approval study is to compare the risk of developing  $\geq$ CIN2 in three years among subjects with positive APTIMA HPV 16 18/45 Genotype results at baseline versus those with negative APTIMA HPV 16 18/45 Genotype results at baseline and at a three-year follow-up period. The absolute risk of  $\geq$ CIN2 (with 95% confidence interval, CI) for each assay result and the relative risk of  $\geq$ CIN2 between subjects with different assay results will be calculated. The APTIMA HPV 16 18/45 Assay is intended as a reflex test for samples from women tested positive for the APTIMA HPV Assay (P100042). Therefore, this post-approval study will be conducted using samples from the ongoing post-approval study for P100042. A total of 10,545 subjects from the premarket study are eligible for the three year follow-up.

Please be advised that the results from this study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years of the study and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies for each study, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" ([www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2)).

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" ([www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm)).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR)

regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at [www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm](http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm).

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at [www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm](http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm).

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at [www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm). Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information:

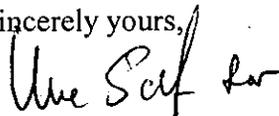
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/ucm134508.htm>; clinical and statistical data:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/ucm136377.htm>)

U.S. Food and Drug Administration  
Center for Devices and Radiological Health  
PMA Document Mail Center – WO66-G609  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Kate Simon at 301-796-6204.

Sincerely yours,



Sally Hojvat, M.Sc., Ph.D.

Director

Division of Microbiology Devices

Office of *In Vitro* Diagnostic Devices and

Radiological Health

Center for Devices and Radiological Health