



Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

Third Wave Technologies, Inc.  
c/o Jorge Garces, Ph.D.  
VP Research and Development  
502 South Rosa Road  
Madison, WI 53719

MAR 12 2009

Re: P080015  
CERVISTA™ HPV 16/18  
Filed: April 28, 2008  
Amended: November 4 and 18, 2008; February 13, 2009; March 10, 2009  
Procode: MAQ

Dear Dr. Garces:

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 Cervista™ HPV 16/18.

Cervista™ HPV 16/18 Indications For Use:

The Cervista™ HPV 16/18 test is an in vitro diagnostic test for the qualitative detection of DNA from Human Papillomavirus (HPV) Type 16 and Type 18 in cervical specimens.

The Cervista™ HPV 16/18 test uses the Invader® chemistry, a signal amplification method for detection of specific nucleic acid sequences. This method uses two types of isothermal reactions: a primary reaction that occurs on the targeted DNA sequence and a secondary reaction that produces a fluorescent signal.

The Cervista™ HPV 16/18 test is indicated:

- 1) In women 30 years and older the Cervista™ HPV 16/18 test can be used adjunctively with the Cervista™ HPV HR test in combination with cervical cytology to screen to assess the presence or absence of high-risk HPV types 16 and 18. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

- 2) To be used adjunctively with the Cervista™ HPV HR test in patients with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results, to assess the presence or absence of high-risk HPV types 16 and 18. 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.

Cervical specimens that may be tested with the Cervista™ HPV 16/18 test include the following preservation system and collection devices:

- ThinPrep® Pap Test™ PreservCyt® Solution
- Broom-type device (e.g. Rovers Cervex Brush, Wallach Papette), 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 described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the periodic reporting requirements outlined in the enclosure, you have agreed to conduct a post-approval study to continue follow-up of the "negative for intraepithelial lesion or malignancy" (NILM) population recruited in the premarket phase of the PMA, which consists of women 30 years old or older with normal cervical cytology who have Cervista HPV 16/18 test results at baseline.

The primary objective of the study is to compare the cumulative 3-year risk of developing cervical intraepithelial neoplasia 2 or higher ( $\geq$ CIN2) disease among women who are 30 years old or older, have a normal cytology result, and are HPV 16/18-positive at baseline against their counterparts who are HPV 16/18-negative at baseline. Additionally, Cervista assay specifications including sensitivity, specificity, positive and negative predictive values will be estimated at study completion.

Subjects will be followed for 3 years and have annual study visits. At each follow-up visit, cervical cytology is performed. Women who have atypical squamous cells of undetermined significance (ASC-US) or higher grade cytology results will have a colposcopy performed, and subsequently a biopsy if needed. Approximately 2,000 subjects were enrolled in the premarket phase of this study, and the study is required to provide data for all subjects who complete the study protocol, allowing for a 50% loss to follow-up rate, thus requiring data on a minimum of 1,000 subjects at the end of follow-up period.

The follow-up period of the study will be completed in March 2011, and the study final report will be submitted to FDA by the end of August 2011. The study protocol DP0517, version 1.6, has been developed and agreed upon by FDA and Third Wave Technologies and Third Wave Technologies submitted it to FDA on March 10, 2009. Post-approval study reports will be submitted every six months for the first two years and then annually until the study is completed. The results of the post-approval study must be reflected in the labeling (via PMA supplement) when the study is completed.

Expiration dating for this device has been established and approved at 12 months when stored between -30°C and -15°C.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available 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 <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 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 requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

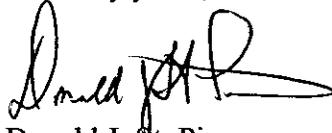
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling 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.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Kate Simon at 240-276-0770.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Donald J. St. Pierre". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Donald J. St. Pierre  
Acting Director  
Office of *In Vitro* Diagnostic Device  
Evaluation and Safety  
Center for Devices and  
Radiological Health

Enclosure

## CONDITIONS OF APPROVAL

**PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT.** Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effectuated" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

**POSTAPPROVAL REPORTS.** Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
  - a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
  - b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

**ADVERSE REACTION AND DEVICE DEFECT REPORTING.** As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.
2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:
  - a. has not been addressed by the device's labeling; or
  - b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. In accordance with the current Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device within the reporting time frames specified in the regulation. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA whenever the manufacturer receives or otherwise becomes aware of information, from any source, that reasonably suggests that one of its 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 <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>