



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Debra J. Rasmussen
Worldwide Executive Director, Regulatory and Quality Affairs
Veridex, LLC
33 Technology Drive
P.O. Box 4920
Warren, NJ 07059

JUL 16 2007

Re: P060017
Device: GeneSearch Breast Lymph Node (BLN) Assay
Received: May 1, 2006
Amended: July 21, August 16, September 12, September 26, and October 12, 2006
and March 14, March 28, April 17, April 26, and July 16, 2007
Procude: OCB

Dear Ms. Rasmussen:

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 GeneSearch Breast Lymph Node (BLN) Assay. This device is indicated as a qualitative, in vitro diagnostic test for the rapid detection of greater than 0.2 mm metastases in nodal tissue removed from sentinel lymph node biopsies of breast cancer patients. Results from the assay can be used to guide the intra-operative or post-operative decision to remove additional lymph nodes. Post-operative histological evaluation of permanent sections of the tissue specimen, in accordance with usual diagnostic practice and using the Veridex lymph node cutting scheme, is required. 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), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the periodic post-market report (often referred to as annual report) requirements outlined in the enclosure, you have agreed to the Conditions of Approval requiring that the company conduct two post-approval studies which are described in items 1 and 2 below.

1. GeneSearch Breast Lymph Nodes (BLN) Assay Positive-Predictive-Concordance (PPC) Study

You will conduct a clinical post-approval study as per the GeneSearch BLN Assay PPC study protocol submitted to FDA on June 15, 2007. The primary objective of the first clinical study is to estimate the positive predictive concordance (PPC) between the BLN assay and histology as routinely practiced, i.e., routine H&E histology of sentinel lymph node(s) (SLN), and when available, routine histology of non-sentinel axillary lymph nodes (ALN). The PPC value is defined as the proportion of BLN assay positive subjects with histologically detectable breast cancer metastases.

The secondary objectives of this study include:

- estimation of the positive predictive value (PPV) against more extensive H&E sectioning
- analysis based on size of metastases
- evaluation of assay invalid result proportion;
- assessment of site-to-site variability of the BLN assay performance
- estimation of PPC and negative predictive concordance (NPC) against SLN routine histology only
- assessment of positive and negative likelihood ratios

You will conduct this study in at least four clinical sites in the United States and enroll a minimum of 1,000 female or male subjects aged 18 years or older previously diagnosed with breast cancer and scheduled for sentinel lymph node biopsy. The study population of at least 1,000 subjects will also include a minimum of 246 BLN positive patients. You have agreed that the study sample size may have to be increased if the disease prevalence in the study population is lower than expected or if the estimated PPC is lower than expected. Subjects will not be included if they have a previous diagnosis of lymphoma or have been treated pre-operatively for breast cancer by either neoadjuvant therapy and/or hormonal intervention. All enrolled subjects are expected to have been counseled on the use of the assay as part of physician-patient discussion of lymph node dissection procedures and complications. Persons performing the GeneSearch BLN assay are expected to have successfully completed training in the assay use prior to using the assay for clinical decision-making. This study will be completed by the sponsor within three years after the date of device approval.

Every 6 months for the first two years and then annually, thereafter, you are to submit a progress report that includes, but is not limited to, the status of patient enrollment and other milestones as it compares to the stated goals and an explanation for any delay in meeting these goals. This requirement is in addition to the annual reporting requirement for the PMA.

2. GeneSearch Breast Lymph Nodes (BLN) Assay Timing Study (TS)

You will conduct a second clinical study with the following objectives:

- to determine, under clinical use conditions, the assay turn-around-time (TAT) from the time of node removal to the report of the assay result to the surgeon
- to determine, under clinical use conditions, whether the assay result was or was not received in time to make an intra-operative decision

- to collect data in relation to other surgical procedures during the sentinel lymph node dissection/breast surgery to determine if the assay TAT resulted in longer surgery time than would have occurred if the assay had not been used

This study will be conducted in a minimum of four clinical sites in the United States and consecutively enroll a minimum of 320 patients as per the GeneSearch BLN Assay TS protocol submitted to FDA on June 15, 2007. Assay TAT will be collected at sites that are using the GeneSearch BLN Assay for intra-operative testing of sentinel lymph nodes. To be eligible to participate in the study, clinical sites will make a commitment to use the assay result to guide the decision to complete an axillary lymph node dissection. Patients will have been diagnosed with carcinoma of the breast and be a candidate for lymph node surgery as per each site's standard of care. The patients may be female or male, at least 18 years-old, and will meet study inclusion criteria described in the protocol. Patients receiving pre-operative therapy for breast cancer, such as neoadjuvant therapy or hormonal intervention are not eligible to participate in this study. Patients should be counseled on the use of the assay before use of the assay as required by the package insert. This study will be completed by the sponsor within 12 months after the date of device approval.

Every 6 months for the first two years and then annually, thereafter, you are to submit a progress report that includes, but is not limited to, the status of patient enrollment and other milestones as it compares to the stated goals and an explanation for any delay in meeting these goals. This requirement is in addition to the annual reporting requirement for the PMA. Draft clinical protocols for both above studies have been received, reviewed, and agreed upon.

Expiration dating for this device has been established and approved at 8 months when stored at -15°C to -25°C , before opening and after opening. Kit is stable for 2 hours at room temperature when in use. Expiration dating for the RNA preparation kit is established at 12 months when stored at $15-25^{\circ}\text{C}$. 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).

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 Federal Food, Drug, and Cosmetic Act (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.

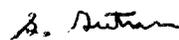
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their 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 James P. Reeves or Robert L. Becker, Jr. at 240-276-1290 or 240-276-0843, respectively.

Sincerely yours,



Steven I. Gutman, M.D., M.B.A.
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 Effected" 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 Effected" 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 Effected." 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.

The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

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 or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Additional information on MDR is available at <http://www.fda.gov/cdrh/devadvice/351.html>