



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125085/91

**FEB 22 2008**

Genentech, Incorporated  
Attention: Todd W. Rich, M.D.  
Vice President, Clinical and Commercial Regulatory Affairs  
1 DNA Way, MS #242  
South San Francisco, CA 94080

Dear Dr. Rich:

Your request to supplement your biologics license application for bevacizumab to include a new indication for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

As requested in your letters of February 8 and 20, 2008, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to further define the degree of clinical benefit to patients. You are required to conduct such studies with due diligence. As stated in 21 CFR 601.43(b), if you fail to meet these requirements, the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval is contingent upon completion of clinical studies as outlined in your letters of February 8 and 20, 2008. This postmarketing study commitment is subject to the reporting requirements of 21 CFR 601.70:

1. To submit an efficacy supplement containing the final study reports (including summary analyses and primary datasets) and revised labeling based on the results from both of the following studies:
  - Study BO17708, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel Plus Placebo as First-Line Treatment for Patients with HER2-Negative Metastatic Breast Cancer." The protocol and a

revised statistical analysis plan were submitted to IND 7023 on January 8, 2008, and February 1, 2008, respectively. The study was completed on February 4, 2008.

- Study AVF3694g “A Multicenter, Phase 3, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer.” The protocol was submitted to IND 7023 on August 14, 2007. Patient accrual has been completed and the study will be completed by February 28, 2009. The supplement will be submitted by July 1, 2009.

We expect you to complete reporting of these studies within the framework described in your letter of February 20, 2008, and summarized above.

For administrative purposes, all submissions related to these postmarketing studies should be clearly designated “Subpart E Postmarketing Study Commitments.”

In addition, we note your following postmarketing commitments, specified in your letter of February 20, 2008, that are not a condition of the accelerated approval. These commitments are:

2. To submit a clinical study report, including summary analyses and primary datasets, for study AVF3693g, “A Phase 3, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer.” The protocol was submitted to IND 7023 on January 9, 2007. Patient accrual will be completed by June 30, 2009, and the study completed by March 31, 2010. The clinical study report will be submitted by January 31, 2011.
3. To submit a clinical study report, including summary analyses and datasets, for study BO20231, “A Randomized, Open-Label, 2-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Trastuzumab/Docetaxel Compared with Trastuzumab/Docetaxel Alone as First Line Treatment for Patients with HER2 Positive Locally Recurrent or Metastatic Cancer.” The protocol was submitted to IND 7023 on February 20, 2007. Patient accrual will be completed by July 31, 2011, and the study completed by April 30, 2012. The clinical study report will be submitted by April 1, 2013.
4. To submit a clinical study report, including summary analyses and datasets, for study CALGB 40503, “A Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Endocrine Therapy Alone or Endocrine Therapy plus Bevacizumab for Women with Hormone-Receptor Positive Advanced Breast Cancer.” The protocol was submitted to IND 7023 on January 19, 2007. Patient accrual will be completed by February 29, 2012, and the study completed by September 30, 2012. The clinical study report will be submitted by December 31, 2013.

Submit all study final reports to your BLA, STN BL 125085. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cder/guidance/5569fn1.htm>) for further information.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125085/91." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

Marketing the product with final printed labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

As required by 21 CFR 601.45, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-

1266. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,

A handwritten signature in black ink that reads "Richard Pazdur MD". The signature is written in a cursive style with a large, prominent "R" at the beginning.

Richard Pazdur, M.D.

Director

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosure: Revised Labeling