DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/85

OCT 1 1 2006

Genentech, Incorporated
Attention: Todd Rich, M.D.
Vice President, Clinical and Commercial Regulatory Affairs
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

Dear Dr. Rich:

Your request to supplement your biologics license application for Bevacizumab to include a new indication for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel 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 indication.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct a postmarketing study as described in your letter of October 11, 2006, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

1. To submit an efficacy supplement containing the final study report, including summary analyses and primary datasets, and appropriate revised labeling describing the effect of overall survival in the entire population and by gender and age from the Hoffman-LaRoche-sponsored study, BO17704 "A Randomized, Double-Blind, Multicenter Phase 3 Study of Bevacizumab in Combination with Cisplatin and Gemcitabine Versus Placebo, Cisplatin and Gemcitabine in Patients with Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy". The protocol was submitted to BB-IND 7023 on February 13, 2006, and patient accrual was completed by August 31, 2006. The study will be completed by June 20, 2008, and the supplement will be submitted by December 31, 2008.

2. To submit a supplement containing a final safety report and appropriate revised labeling describing the adverse event profile of Bevacizumab administered to patients with previously treated central nervous system (CNS) metastases. The supplement will contain information on an integrated safety population of least 50 patients with

previously treated CNS metastases enrolled on studies AVF3752g and AVF3671g to include the summary safety analyses, primary datasets with demographic, treatment and safety information, case report forms for all deaths and dropouts, narrative summaries for all patients with serious adverse events in either study. For those patients enrolled in study AVF3752g, the supplement will contain information on the number and size of brain metastases. Protocol AVF3752g was submitted to BB-IND 7023 on November 30, 2005. Protocol AVF3671 will be submitted by November 30, 2006, accrual of the minimum number of 50 patients will occur by January 31, 2008, and the supplement will be submitted by March 31, 2008.

3. To submit a safety update on an annual basis containing safety information summarizing and characterizing NCI-CTC version 3 Grade 2-5 adverse events involving the CNS from the following three placebo-controlled, randomized studies: OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). For studies which have not been completed, the annual safety update will be prepared by an independent, unblinded data coordinating center that will not share information with any individual involved in the design, conduct, and analysis of the trials. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005, and protocol AVF3693g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006. Annual reports will be submitted by December 31, 2007, December 31, 2008, and December 31, 2009.

4. To submit a supplement containing a final safety report and revised labeling, if applicable, based on data from a minimum of 100 patients with CNS metastases (roughly half of whom were randomized to Bevacizumab plus additional anti-cancer agents) enrolled in studies OSI3364g, AVF3693g, and AVF3995g. The supplement will include summary analyses and primary datasets, including the number and size of CNS metastases for each patient. A statistical analysis plan for the integrated summary analyses will be submitted by June 30, 2007, and the supplement will be submitted by December 31, 2010.

5. To conduct a sub-study to address the impact of Bevacizumab on the QT interval. This sub-study will be added to three planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The sub-study will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Bevacizumab-treated patients and 60 controls will be evaluated in this sub-study. A detailed protocol for this sub-study will be submitted by January 31, 2007. The sub-study will be initiated by June 30, 2007 and will be completed by June 30, 2010. A final study report and revised labeling, if applicable, will be submitted by December 31, 2010.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125085. 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 Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

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/5569fnl.htm) for further information.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. The final printed labeling (FPL) must be identical to the enclosed labeling text dated October 11, 2006. Marketing product with FPL that is not identical to the approved labeling may render the product misbranded and an unapproved new drug. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments 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. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

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 submit within 30 days 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 dated October 11, 2006. Upon receipt and

verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.
Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.
Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

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

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: Revised Labeling