DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

FEB 2 6 2004

Our STN: BL 125085/0

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs, Quality and Compliance
1 DNA Way MS#48
South San Francisco, CA 95080

Dear Dr. Garnick:

We have approved your biologics license application for Bevacizumab effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Bevacizumab under your existing Department of Health and Human Services U.S. License No. 1048. Bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for the first-line treatment of patients with metastatic carcinoma of the colon and rectum.

Under this authorization, you are approved to manufacture Bevacizumab at your facility in South San Francisco, CA. You may label your product with the proprietary name AVASTIN and will market it as a 4 mL vial containing 100 mg (25 mg/mL) and as a 16 mL vial containing 400 mg (25 mg/mL).

The dating period for Bevacizumab shall be 18 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 24 months when stored at -20°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug product and drug substance under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Bevacizumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Bevacizumab, or in the manufacturing facilities.

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 deferring submission of your pediatric study until December 31, 2006. Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below:

1. To obtain preliminary safety and activity data and to characterize the pharmacokinetics of Bevacizumab in pediatric patients in Study AVF2117s, a Phase 1, dose-escalation trial, enrolling up to 24 children with relapsed or refractory solid tumors to be conducted by the Children's Oncology Group (COG). Safety data will include an assessment of the effect of Bevacizumab on growth and development, including fertility. Patient accrual will be completed by December 31, 2005, the study will be completed by March 31, 2006, and the final study report submitted by December 31, 2006.

For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitments".

In addition, we acknowledge your other written commitments as described in your letter of February 26, 2004, as outlined below:

Additional Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

2. To collect data and conduct analyses within study NO16966 that will characterize the clinical consequences of both full-dose and low-dose anticoagulation therapy and assess the role of the international normalization ratio (INR) as a predictor of subsequent hemorrhage and/or thrombosis in patients treated with Bevacizumab. This will be evaluated in a subset of 1320 subjects, enrolled in the amended study NO16966, 50 percent of whom will be randomized to receive Bevacizumab. The final protocol will be submitted by March 31, 2004, patient accrual will be completed by June 30, 2005, the study will be completed by March 30, 2007, and the final study report submitted by September 28, 2007.

3. To conduct analyses to characterize the comparative incidence of proteinuria, risk factors associated with proteinuria, and the clinical course of proteinuria (including time to resolution) using available data from ongoing trials AVF2107g, AVF2192g, and AVF2119g. Collection of data under these studies will be completed by June 30, 2004, an analysis post-last patient observed will be submitted by December 31, 2004, the one year follow-up period will be completed by June 30, 2005, and an analysis post-one year follow-up will be submitted by December 30, 2005.

4. To assess for risk factors associated with proteinuria by prospectively collecting and analyzing data to characterize the incidence and clinical course (including duration) of proteinuria in patients during treatment with Bevacizumab and following the discontinuation of Bevacizumab and in concurrent control patients. This will be

evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, this portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

5. To explore patient factors associated with the risk of development of proteinuria, characterize the clinical course of proteinuria, and assess screening strategies that more accurately identify patients at increased risk of high-grade proteinuria and nephrotic syndrome in 100 patients treated with Bevacizumab alone or in combination with (b)(4) in study AVF2938g. The data will be analyzed by overall study population and by treatment arm. The final protocol will be submitted by March 31, 2004, patient accrual will be completed by March 31, 2005, the study will be completed by March 31, 2006, and the final study report submitted by September 29, 2006.

6. To conduct analyses to characterize the comparative incidence of hypertension in patients treated with Bevacizumab to those not receiving Bevacizumab, risk factors associated with hypertension, and the clinical course of hypertension (including time to resolution), using available data from studies AVF2107g, AVF2192g, and AVF2119g. Collection of data under these studies will be completed by June 30, 2004, an analysis post-last patient observed will be submitted by December 31, 2004, the one year follow-up period will be completed by June 30, 2005, and an analysis post-one year follow-up will be submitted by December 30, 2005.

7. To prospectively collect and analyze data characterizing the incidence and clinical course (including duration and medical management) of hypertension in patients during treatment and following the discontinuation of Bevacizumab and in concurrent control patients. This will be evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, this portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

8. To provide narrative descriptions of each vascular adverse event (myocardial infarction, cerebrovascular accident, peripheral arterial event, vascular aneurysm or other vessel wall abnormalities, and venous thromboembolic events) for patients enrolled in study AVF2540g and to provide descriptive statistics of the incidence of vascular events (overall and each subtype). Patient accrual will be completed by June 30, 2004, the study will be completed by December 31, 2004, and the final study report submitted by June 30, 2005.

9. To collect data and conduct analyses of the comparative incidence of delayed vascular events (myocardial infarction, cerebrovascular accident, peripheral arterial event, vascular aneurysm or other vessel wall abnormalities, and venous thromboembolic events) in Bevacizumab-treated patients following the discontinuation of Bevacizumab

(from 12 to 24 months after initiation of treatment) and in concurrently enrolled control patients (over the same time interval-12 to 24 months after initiation of treatment) in NSABP study C-08. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, this portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

10. To assess the relative impact on fertility and gonadal function of Bevacizumab in combination with chemotherapy, as compared to patients receiving chemotherapy alone. This will be evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, the portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

11. To examine the long-term impact of Bevacizumab on pregnancy outcome. This will be evaluated through inclusion of a special section in the periodic adverse experience report (PAER) containing a thorough and cumulative evaluation of pregnancy, spontaneous abortion, and fetal malformation. The PAER will be submitted at quarterly intervals for three years from the date of approval. This commitment will be fulfilled by submission of a final PAER by February, 28, 2007.

12. To directly assess the pharmacokinetic interactions between irinotecan and Bevacizumab in a single-arm, cross-over study in approximately 32 evaluable subjects. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 30, 2005, the study will be completed by March 31, 2006, and the final study report submitted by September 29, 2006.

13. To assess the pharmacokinetic profile of Bevacizumab in a rodent model of hepatic dysfunction. The final protocol will be submitted by March 31, 2004, the study will be initiated by June 30, 2004, completed by September 30, 2004, and the final study report submitted by December 31, 2004.

14. To perform additional analyses of clinical pharmacokinetic data from studies AVF0780g and AVF2107g in order to provide a comparison of clearance in patients with hepatic dysfunction. The results of these additional analyses will be submitted by June 30, 2004.

15. To obtain further information on the pharmacokinetics of Bevacizumab by assessing Bevacizumab drug levels at 3 and 6 months post-treatment in NSABP study C-08. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, the pharmacokinetic evaluation will be completed by

June 30, 2008, and the population pharmacokinetics final study report submitted by December 31, 2008.

16. To develop a standardized approach to the collection of data and generation of narrative descriptions of selected adverse events (gastrointestinal perforation, intra-abdominal abscess, fistula, wound dehiscence) that will include description of the event, surgical operative and pathology reports, and outcome/resolution information, for all such patients enrolled in studies NO16966 and NSABP study C-08. The summary report for this data will be submitted by June 30, 2008.

17. To provide the final study report for study E3200, examining the comparative safety and effectiveness of single agent Bevacizumab, Bevacizumab in combination with the (b)(4) regimen, and (b)(4) alone. The study will be completed by September 30, 2005 and the final study report submitted by March 31, 2006.

18. To provide the study report for study AVF2192g examining the comparative efficacy and safety of 5-fluorouracil and leucovorin with and without Bevacizumab in patients with newly diagnosed metastatic colorectal cancer who are unable to tolerate irinotecan-based therapy. The final study report will be submitted by September 30, 2004.

19. To develop a validated, sensitive and accurate assay for the detection of an immune response (binding and neutralizing antibodies) to Bevacizumab, including procedures for accurate detection of antibodies to Bevacizumab in the presence of serum containing Bevacizumab and vascular endothelial growth factor. The assay methodology and validation report will be submitted by September 30, 2004.

20. To more accurately characterize the immune response to Bevacizumab in NSABP study C-08 using the more sensitive, validated assay described above. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, the study will be completed by June 30, 2008, and the final study report submitted by December 31, 2008.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:

21. To re-evaluate the release and shelf-life specifications for Bevacizumab Drug Substance and Drug Product based upon tolerance intervals on a yearly basis to reflect increased manufacturing experience. The cumulative data and analysis for product manufactured up to and including 2004 will be provided in the February 2004 to February 2005 Annual Report to be submitted by April 30, 2005.

22. To perform *in vitro* and *in vivo* viral and adventitious agent testing on a current (b)(4) scale production lot of Bevacizumab at a cell age of (b)(4) of the master cell bank to validate the (b)(4) limit of *in vitro* age that was established in small-scale studies. The testing will be completed by June 30, 2004, and the final study

report submitted as part of the February 2004 to February 2005 annual report to be submitted by April 30, 2005.

23. To perform genetic stability testing on a current (b)(4) scale production lot of Bevacizumab at a cell age of (b)(4) of the master cell bank to validate the (b)(4) limit of *in vitro* age that was established in small-scale studies. The nucleotide sequence of the integrated bevacizumab expression construct coding for the correct amino acid sequence in the aged cells will be verified by peptide mapping with 100% sequence coverage. The testing will be completed by June 30, 2004, and the final study report submitted as part of the February 2004 to February 2005 annual report to be submitted by April 30, 2005.

24. To perform and submit a formalized assessment of the overall risk of cross-contamination between (b)(4) derived products that could result from sharing product-contacting equipment and parts by June 30, 2004.

25. To modify your practices in accordance with the risk assessment as stated in commitment 24 by providing an implementation plan for any modifications and a justification for any continued sharing of minor process equipment and parts by September 30, 2004.

26. To develop control measures (e.g., equipment, procedures and training) to ensure that hoses that are exposed to process fluids are dedicated to either (b)(4) process areas. These measures will be implemented by December 31, 2004.

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 nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BLA 125085. If the information in the final study report supports a change in the labeling, the final study report should be submitted as a supplement. We may also request a supplement if we think labeling changes are needed. 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), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publically disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

In addition, we understand that you will maintain on stability the 1000 mg vialed drug products to the intended length of expiry in order to support the bracketing of the 400 mg drug product configurations. We acknowledge that drug product lots R9078A, R9084A, and R9085A will be maintained on the stability program.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81). You should submit distribution reports to CBER Document Control Center, Attn: Office of Therapeutics Research and Review, Suite 200N (HFM-99), 1401 Rockville Pike, Rockville, MD 20852-1448

You must submit reports of biological product deviations under 21 CFR 600.14. You promptly should identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of

Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. 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 Division of Drug Marketing, Advertising and Communications (HFD-42), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. 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.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Sincerely,

(b)(6)

Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Labeling