DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103792/5150

NOV 16 2006

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

Dear Dr. Rich:

Your request to supplement your biologics license application for Trastuzumab as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, for the adjuvant treatment of patients with HER2-overexpressing, node-positive 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.

We acknowledge your written commitments to conduct postmarketing studies as described in your letter of November 2, 2006, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To provide a final study report at the time of the final analysis of overall survival (analysis based on 710 deaths) in accordance with the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The final study report should include the primary datasets and programs for generation of analyses and all subset analyses for the final analysis of overall survival and an updated analysis of disease-free survival, including exploratory analyses in subgroups based on the timing and type of hormonal treatment administered to patients. The 710th death is expected to occur by September 30, 2011, and the final study report will be submitted by September 30, 2012.

2. To provide final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility over the immediate post-treatment period (18 months from initiation of adjuvant chemotherapy) in all patients enrolled as of the termination of study enrollment in April 2005.
The final study report should include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The completion of this aspect of the integrated study (18 months from the April 2005 termination of accrual) is October 31, 2006, and the final study report will be submitted by May 31, 2008.

3. To provide interim cardiac safety updates on an annual basis beginning on September 30, 2006, as the first cut-off date and ending with a final comprehensive cardiac safety analysis report submitted by September 30, 2012. Each annual cardiac safety update will include a detailed narrative summary of each new clinical event with associated radiologic reports and laboratory findings for all patients enrolled as of the termination of study enrollment in April 2005. The first annual cardiac safety update will be submitted by April 28, 2007. The final comprehensive cardiac safety analysis will be included in the final study report based on 710 deaths. In addition, the final comprehensive study report will contain primary datasets for the ITT population and summary analyses that include, but are not limited to, the analyses described in the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831.

4. To provide a final study report characterizing the safety profile of the two studies among patients who received at least one dose of protocol-prescribed therapy as of the termination of study enrollment in April 2005. The study report will contain primary datasets that include final study data for all patients who received at least one dose of protocol-specified treatment and summary analyses that include, but are not limited to, the analyses described the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The datasets should include study drug information sufficient to characterize exposure in each patient for the individual study drug components, including dose modification (reduction or suspension of dosing) and should provide the timing of the events in relation to specific study drug treatment. The database should also contain a flag to distinguish those patients who were included in the joint analysis ITT population in the original database from those patients who were not included in this population. The completion of this aspect of the integrated study (18 months from the April 2005 termination of accrual) is September 30, 2006, and the final study report will be submitted by May 31, 2008.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103792. Submit non-clinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103792. 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 Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post130.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 for the package insert) submitted November 8, 2006. Marketing product with FPL that is not identical to the approved labeling text 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.

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 November 8, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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.

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

Enclosure: Final Printed Labeling