DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STNs: BL 103792/5187 and 103792/5189

MAY 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 94080-4990

Dear Dr. Rich:

Your request to supplement your biologics license application for trastuzumab (Herceptin) to expand the breast cancer indication as follows has been approved:

- Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer (BL 103792/5187).

- Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer (BL 103792/5189).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for these supplements because necessary studies are impossible or highly impracticable. HER2 over-expressing, node-positive or high-risk node-negative, breast cancer does not occur in pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biologic product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Herceptin was first approved in 1998 as a single agent for HER2 over-expressing metastatic breast cancer, in patients who have received one or more chemotherapy regimens for metastatic disease. It was also approved in combination with paclitaxel for the first-line treatment of HER2 over-expressing metastatic breast cancer. The label for Herceptin has a black box warning concerning cardiomyopathy. Now, however, Herceptin is being approved as a component of two novel adjuvant treatment regimens for patients with HER2 over-expressing, node-positive or high-risk node-negative, breast cancer following surgical resection, and our recent analysis of the data in your supplements indicate the need to assess the long-term cardiovascular risks of Herceptin in these new treatment situations. Our new analysis of available scientific data indicates that the long-term incidence and severity of the known serious risk of cardiovascular toxicity associated with Herceptin may be different with the use of this drug in new combination with these adjuvant chemotherapy regimens. In addition, based on new information associated with the fact that Herceptin will now be indicated for use with Carboplatin, we are concerned that the use of Herceptin with Carboplatin may cause a drug-drug interaction (DDI) that could affect the pharmacokinetics of one or the other of the two drugs, creating an unexpected serious risk.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of cardiovascular toxicity in the new patient population and when the drug is used in combination with other therapies, or assess the potential for an unexpected serious risk associated with an effect on pharmacokinetics from the use of Herceptin in combination with Carboplatin.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess either this known serious risk or the potential for this unexpected serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk or the potential for this unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical trials of Herceptin:

1. To provide an update of cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic cardiac event.

   The timetable you submitted on April 24, 2008, states that you will conduct this trial according to the following schedule:

Completion of 5-year follow-up:	June 30, 2009
Final Report Submission:	March 31, 2010

2. To perform a DDI trial in metastatic cancer patients to evaluate the impact of Herceptin on Carboplatin pharmacokinetics and to evaluate the impact of Carboplatin on Herceptin pharmacokinetics. Herceptin concentrations in the DDI trial will be compared to clinical pharmacokinetic data from clinical trials BO16348, BO15935, and WO16229.

   The timetable you submitted on May 13, 2008, states that you will conduct this trial according to the following schedule:

Protocol submission:	March 31, 2009
Study Initiation:	September 30, 2009
Final report submission:	January 31, 2013

We acknowledge your written commitment to complete a drug-drug interaction (DDI) trial as described in your May 13, 2008, electronic correspondence (email).

Submit the protocol for continued assessment of cardiac safety and your DDI trial protocol to your IND 4517 with a cross-reference letter to your BLA, STN 103792. Submit all final report(s) to your BLA, STN 103792.

Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of these postmarketing clinical trials pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 601.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Herceptin.

POSTMARKETING STUDY COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70.

We acknowledge your written commitment to provide additional information on the ongoing BCIRG006 study as described in your April 24, 2008, letter as outlined below:

3. To provide an update of efficacy from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 10 years of follow-up, with an interim update of efficacy at 5-years of follow-up.

   The timetable you submitted on April 24, 2008, states that you will conduct this trial according to the following schedule:

Completion of 5-year follow-up:	June 30, 2009
5-year DFS and OS update	March 31, 2010
Completion of 10-year follow-up	June 30, 2014
Final report submission (10-year DFS and OS update)	March 31, 2015.

Submit the protocol to your IND 4517, with a cross-reference letter to your BLA, STN 103792. Submit all final report(s) to your BLA, STN 103792. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- Postmarketing Commitment Protocol
- Postmarketing Commitment - Final Report
- Postmarketing Correspondence
- Annual Status Report of Postmarketing 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/5569fnl.htm) for further information.

CONTENT OF LABELING

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 these submissions "Product Correspondence – Final SPL for approved STN BL 103792/5187 and 103792/5189." 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.

You may 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 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.

If you have any questions, call Monica L. Hughes, M.S., RPM, at 301-796-2320.

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: Package Insert Labeling

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