



Our STN: BLA 103792/5250

SUPPLEMENT BLA APPROVAL

Genentech Incorporated
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way, MS#241B
South San Francisco, CA 94080

October 20, 2010

Dear Dr. Rohrer:

Please refer to your Supplemental Biologics License Application (sBLA), dated April 19, 2010, received April 20, 2010, submitted under section 351 of the Public Health Service Act for Herceptin (trastuzumab).

We acknowledge receipt of your amendments dated May 20, 2010, June 25, 2010, July 8, 2010, July 16, 2010, August 6, 2010, August 13, 2010, August 19, 2010, August 23, 2010, September 14, 2010, October 8, 2010, October 12, 2010, October 18, 2010, October 19, 2010, and October 20, 2010.

This "Prior Approval" efficacy supplement to your biologics license application proposes to include a new indication for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103792/5250.**"

Also within 14 days, amend all pending supplemental applications for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Herceptin (trastuzumab) was approved on September 25, 1998, we have become aware of a failure in the expected pharmacologic action of Herceptin (trastuzumab) (i.e., low Herceptin trough concentrations that resulted in decreased overall survival in 25% of patients treated for gastric cancer). The safety risk includes subjecting patients to the known serious toxicities of Herceptin (trastuzumab), including cardiomyopathy, exacerbation of chemotherapy-induced neutropenia and febrile neutropenia, infusion reactions, and pulmonary toxicity, including interstitial pneumonitis and acute respiratory distress syndrome, without the expected pharmacologic benefit of a clinically significant increase in survival. This new safety data was provided in your efficacy supplement submitted April 19, 2010, that contained data from Protocol BO18255, a randomized trial of cisplatin and a fluoropyrimidine with or without Herceptin (trastuzumab) in patients with gastric cancer over-expressing HER2/neu. Therefore, we consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

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 a signal of a serious risk of failure in the expected pharmacologic action of Herceptin (trastuzumab) resulting in decreased survival in 25% of patients treated for gastric cancer.

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 this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #1

To develop a validated assay for Herceptin (trastuzumab) pharmacokinetic measurements for use by clinical sites participating in the trial required under PMR #2, for purpose of identifying patients who require an alternate dosing regimen.

PK Assay Validation Report Submission:	01/11
Validated PK assay to Support Clinical Sites:	01/12

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of failure in the expected pharmacologic action of Herceptin (trastuzumab) resulting in decreased survival in 25% of patients treated for metastatic gastric cancer.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #2

To evaluate the safety and tolerability of an alternate Herceptin (trastuzumab) dosing regimen that ensures that all patients, inclusive of patients with a Herceptin C_{min} of ≤ 12 mcg/mL on Cycle 1 Day 21 after an initial dose of 8 mg/kg, achieve adequate exposure as reflected by C_{min} of at least 12 mcg/mL by Cycle 2 Day 21, and maintain the exposure level throughout the treatment period. This may be achieved either through a specified regimen applied to all patients or through an individualized, pharmacokinetically guided treatment strategy. The pharmacokinetics and tolerability of the alternate Herceptin (trastuzumab) dosing regimen in patients with HER2-overexpressing, metastatic gastric cancer will be determined in a pharmacokinetic trial that enrolls an adequate number of patients to provide an initial assessment of safety.

The timetable you submitted on October 18, 2010 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/11
Study Initiation:	01/12
Submission of Interim PK Analysis:	05/13
Sample Size Re-estimation:	09/14
Submission of Interim OS Analysis:	12/15
Completion of Patient Accrual:	12/16
Trial Completion:	06/18
Final Report Submission:	12/18

PMR #3

To conduct a clinical trial of Herceptin (trastuzumab) in combination with standard chemotherapy, in patients with previously untreated, HER2 overexpressing, metastatic gastric cancer, if the pharmacokinetic trial (PMR #2) definitively demonstrates that the higher Herceptin dose improves efficacy among patients with low exposure after the initial dose, but

does not provide adequate safety and efficacy data among patients with higher exposure to support a new dosing regimen for all patients. The objective of the trial will be to further compare the effect of overall survival in patients who demonstrate adequate exposure after one cycle of the approved Herceptin dosing regimen, as determined by a validated assay for Herceptin levels, between those randomized to receive the approved dose and schedule (as evaluated in Trial BO18255) for subsequent treatment cycles and those randomized to receive the investigational (alternate) Herceptin regimen evaluated in the pharmacokinetic trial in PMR #2. The trial will be designed to establish that the alternate dosing regimen is not inferior to the dosing regimen approved for the treatment of gastric cancer with a primary endpoint of survival. A secondary endpoint will be to further characterize the safety profile of the alternate dosing regimen.

The timetable you submitted on October 18, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/19
Trial Completion:	10/24
Final Report Submission:	10/25

Submit the protocol to your IND 4517, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Mona Patel, Regulatory Project Manager, at (301) 796-4236.

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